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BRAIN.

PART 2, VOL. 61.

SOME OBSERVATIONS ON HEADACHE.

BY D. W. C. NORTHFIELD.

(From the Department of Neuro-Surgery of the London Hospital.)

HEADACHE is an exceedingly common complaint from which most persons have suffered. In spite of, or perhaps by reason of, its occurrence as a symptom of disease in various parts of the body, the mechanism of its production remains obscure. Such a problem is most likely to be solved by the detailed study of a small group of cases. In this discourse, the study of headache will be limited almost entirely to cases of intracranial tumour, which form a subject conspicuously favourable for clinical research. The lesion is unequivocal and is frequently amenable to operative removal. The investigation of the patient and subsequent operation under local anæsthesia provide many opportunities for the experimental production of headache.

CLINICAL FEATURES.

Although many persons have difficulty in expressing adequately the discomforts and pains they experience, the headache due to a space occupying intracranial lesion is truly one of pain or intense discomfort. It is frequently described as a dull or throbbing ache, a bursting, burning, or sharp stabbing pain, the patient often giving some graphic comparison, such as "it is like a vice closing on my temples" or "it is like something opening and shutting in my head." The pain is usually referred vaguely to the interior of the skull across the forehead, through the temples, or in the occipital region. It may be quite generalized, or may affect only one side, and during the course of the illness it may shift from one area to

[1] This paper formed the basis of a Hunterian Lecture delivered at the Royal College of Surgeons on February 10, 1937. The work has been performed during the tenure of the Will Edmonds Clinical Research Fellowship.

another. In patients in whom the tumour arises in the posterior cranial fossa the complaint of pain and stiffness in the muscles of the neck is particularly common, and this symptom tends also to develop sooner or later if the tumour be situated in other parts of the skull.

There are interesting details concerning the time of onset of headache, and factors which cause its aggravation. It has a predilection for occurring in the morning, usually immediately the patient wakes, but it often wakens him at an unusually early hour. Rising from bed makes it much worse, or the change in posture may bring on the headache if it is not already present. The majority of patients choose to lie in bed with the head only slightly raised and only a few prefer to sit bolt upright. In all cases it is the sudden *change* of posture which seems to be resented. Movement of the head on the neck is liable to increase or precipitate a headache, and this is especially noticeable when the pain is in the back of the head. In such a case examination will usually demonstrate tenderness and spasm of the suboccipital muscles.

One variety of headache may occur which I believe to be pathognomonic of intracranial tumour. This pain is generalized, paroxysmal, and apparently agonizing, causing the patient to writhe and to scream, and to hold his head in his hands. He becomes unco-operative and is deaf to the observer's questions. Indeed, this type of headache not infrequently ends in semiconsciousness, and there may be amnesia of the attack. I choose the term paroxysm deliberately, for the spasm of pain comes on quite suddenly in a patient previously free from headache, and in the course of a second or so attains its maximum intensity. It may last from thirty seconds up to half an hour and then may disappear as quickly as it came, leaving the patient exhausted.

Such a headache, especially when associated with semiconsciousness, is usually confined to the terminal stages of the disease, when it may recur several times in the day. Indeed, its presence should be viewed with alarm, for it indicates a state in which the patient may die, either suddenly or after passing into coma. The urgency of this dangerous state cannot be over emphasized, and this point is well illustrated in the following case, in which the paroxysm of headache ended in an epileptiform attack.

A man, aged 34, had had slight headaches for three years, which had become much more severe in the last six months, and were situated all over the head. After admission to hospital the attacks of headache increased in frequency, and ultimately six occurred in five hours, three within a period of ten minutes. Observed on one occasion, the headache appeared to be paroxysmal, exacerbations every minute causing him to rub his head and to cry out "My head! my head!" Squirming movements of the limbs were present, with a tendency to adversive rotation of the

body to the left. In one of the terminal attacks there was most intense headache, a complaint of vertigo—when he nearly fell out of bed in attempting to compensate for it—adversive movements, and semiconsciousness eventually developed. Each attack lasted about two minutes, and there was complete amnesia for it.

In consequence of the very frequent recurrence of these headaches operation was immediately performed. The intraventricular pressure was over 600 mm. and the dura mater stony hard. A tumour was disclosed situated in the right parietal lobe and was partially removed. The brain was under great tension and in a state of intense hyperæmia, consequently severe hæmorrhage occurred, but the patient made a satisfactory recovery.

Paroxysmal headache occurs in a wide variety of cases including such tumours as glioma of the basal ganglia, acoustic neurinoma, chordoma of the base of the skull, suprasellar cyst, hæmangioma of the cerebellum and colloid cyst of the 3rd ventricle. Only in these rare benign tumours of the 3rd ventricle is paroxysmal headache observed sufficiently frequently to constitute an item of evidence for correct localisation.

What is the chronological incidence of headache in intracranial tumour? Of 100 unselected case records of verified tumours in the London Hospital, in 36 headache was the initial symptom, or it developed at the same time as other complaints (Chart 1). This figure corresponds closely

CHART 1.

THE INCIDENCE OF HEADACHE AS THE INITIAL SYMPTOM IN CASES OF VERIFIED INTRACRANIAL TUMOUR

in	36 out of 100	unselected cases	= 36 per cent.
in	0 out of 9	cases of acoustic neurinoma	= 0 per cent.
in	10 out of 12	other cases of posterior fossa tumour	= 83 per cent.
in	13 out of 37	cases of cerebral glioma	= 35 per cent.
in	5 out of 14	cases of cerebral meningioma ...	= 36 per cent.
in	8 out of 28	cases of frontal lobe tumour	= 29 per cent.
in	7 out of 17	cases of temporal lobe tumour ...	= 41 per cent.

with that of Dowman and Smith (1928). Further analysis is illuminating. In the 100 cases, there were 9 acoustic tumours and in none of these was headache the first symptom. But in 12 other cases of posterior fossa tumour, mainly cerebellar gliomas and hæmangiomas, headache was the first symptom in 10. There were 37 gliomas of the cerebral hemisphere, and in 13 headache was the first symptom, and it is noteworthy that the proportion was approximately the same for meningiomas, 5 out of 14. Considerable discrepancy was found between the incidence of headache as the first symptom in temporal lobe and in frontal lobe tumours. Whereas in temporal tumours headache was the first symptom in 7 out of 17 cases, in frontal tumours it was the first symptom in only 8 out of 28

cases. From ventriculography, we know that temporal tumours cause considerable displacement of the 3rd ventricle, and are very liable to produce hydrocephalus. If these figures are large enough to have statistical value, it is clear that headache is likely to precede other symptoms in those cases in which the tumour, by reason of its location, tends to impede the flow of cerebrospinal fluid through the ventricular system. In an acoustic tumour, however, because of its intimate relation to certain cranial nerves, focal signs will precede headache.

Headache is nearly always referred to the forehead, whether or not it involves other areas as well (Chart 2). It is worth noting that out of a total

CHART 2.

THE DISTRIBUTION OF THE PAIN

FRONTAL HEADACHE

with or without involvement of other areas was present in
95 per cent. of cases of supratentorial tumour.
75 per cent. of cases of infratentorial tumour.

PAIN IN THE NECK

with or without involvement of other areas was present in
22 per cent. of cases of supratentorial tumour.
49 per cent. of cases of infratentorial tumour.

UNILATERAL HEADACHE

Of 42 cases

in 6 the tumour was in the middle line.
in 32 the tumour was situated on the same side as the headache.

N.B.—In only 4 cases was the headache on the side opposite to the tumour.

of 121 cases excluding pituitary adenomas, frontal headache was absent in only 5 per cent. of cases of supratentorial tumour, as compared with 25 per cent. where the tumour was infratentorial. Pain in the neck was present in 22 per cent. of supratentorial tumours and in 49 per cent. of infratentorial tumours. This pain in the neck associated with muscular spasm is usually observed in its severest form when the tumour occurs low in the posterior fossa, forming a tongue which plugs the foramen magnum. A similar mechanism doubtless operates when the tumour is situated elsewhere, for the cerebellar tonsils may be herniated through the foramen magnum, at times to a level as low as the 2nd cervical vertebra. The painful muscular spasm is probably caused by the pressure of the tumour or the tonsils on the posterior roots of the upper cervical nerves.

In 42 patients the headache was entirely or predominantly unilateral

and did not shift from side to side. In six of these the tumour was situated approximately in the middle line, but it is noteworthy that in only four cases was the tumour found to be on the side opposite that affected by headache. These were two cases of frontal and one of parietal meningioma, and one case of abscess of the frontal lobe.

Headache due to an adenoma of the pituitary gland is of a special type. It is frequently more severe in acromegaly, though it never becomes a paroxysm of agony. The pain may be merely a dull ache, or actually throbbing over the forehead and through the temple. Rarely it may spread to the occiput. In contrast to the headache resulting from other tumours, it is frequently associated with, or replaced by, pains described as neuralgia, related to one or both eyes, in the eyebrow, or in some portion of the face. This pain does not progressively involve larger areas of skin supplied by the trigeminal nerve, as with a tumour of the middle cranial fossa or of the Gasserian ganglion, or with large aneurysms of the internal carotid artery.

The Intracranial Pressure During Headache.

It is commonly accepted that the headache produced by an intracranial tumour is due to the increase in the intracranial tension. When the patient is resting horizontally in the lateral position, the pressure of the cerebrospinal fluid in the lumbar theca is identical with the pressure in the ventricles. Of a series of 102 verified cases of tumour, in 63 the pressures exceeded the normal of 100 to 200 mm. of fluid. The highest was an intraventricular pressure exceeding 700 mm., during gas, oxygen and ether anæsthesia. Ether, even in small proportions elevates the pressure slightly, but this was amply offset by the loss of fluid while the manometer was being connected to the needle. The cases which appear to me vitally important to the subject under discussion, are those in which the pressure was not raised. In 39 the pressure was less than 200 mm., and in 16 it was actually *below* 100 mm. Many of these cases with normal or subnormal pressures had been experiencing very severe headache during the period immediately prior to the investigation. In many patients however, headache may be absent although the intracranial pressure is very high. It will be instructive to consider some of these cases in detail (Chart 3). In each, the operation was performed under a local anæsthetic.

Many more similar observations could be mentioned, but these are sufficient to demonstrate that the absolute value of the intracranial pressure bears no relation to the presence or absence of headache. Although headache is clearly related to those diseases which induce an increase in

the intracranial pressure, the high pressure in itself is probably not the cause of the headache. I hope later to prove that headache readily occurs as a result of any sudden *alteration* of pressure, whether an increase or a decrease.

CHART 3.

THE RELATION BETWEEN HEADACHE AND INTRACRANIAL PRESSURE

Of 102 cases of verified intracranial tumour
in 63 cases the pressure exceeded 200 mm.
in 39 cases the pressure was less than 200 mm.
in 16 cases the pressure was less than 100 mm.

Case	*Headache*	*Pressure*
1	severe	low
2	severe	low
3	absent	high
4	absent	high
5	absent	high
	severe	low
6	absent	high
	severe	high

(1) A patient with a tuberculoma of the cerebellum suffered from severe bouts of headache and pain in the neck. At operation the ventricular pressure was so low that the fluid did not rise to the mouth of the needle.

(2) In a patient with a cystic glioma of the frontal lobe, four paroxysms of headache occurred a few hours before the ventricles were tapped; the ventricular pressure was only 40 mm.

(3) A patient with severe chronic hydrocephalus had been perfectly free from headache during the week immediately preceding ventriculography at which the pressure was 600 mm.

(4) In a patient with a frontal meningioma, and who was experiencing no headache at the time, the ventricular pressure was 400 mm.

(5) In a patient with a cerebellar glioma, the ventricular pressure at the beginning of the operation was 430 mm., when he had no headache. Later in the operation he complained of severe headache, but the pressure was zero.

(6) The pressure was over 300 mm. in a patient with a colloid cyst of the third ventricle, during a period of freedom from headache. Five years later, after a long interval of well-being, when headache was severe, the pressure was still over 300 mm.

Such considerations as these cast doubt upon the commonly accepted views that the headache of a brain tumour arises from stimulation of the dura mater by the increased intracranial pressure. The following cases offer further support for this attitude.

A man, aged 32 years, was first admitted to hospital in November, 1932. He had suffered from headaches for four years; they started in the back of the neck, spreading forward around the temples and settling in the middle of the forehead,

occurring regularly in the morning on getting out of bed. For eleven months there had been epileptiform seizures of a generalized type. Papillœdema and localizing neurological signs were absent. In the radiogram of the skull could be detected a small area of pathological calcification in the right temporal lobe; encephalography revealed undilated ventricles, the right lateral ventricle was a little narrower than the left and the system was slightly displaced to the left.

A diagnosis of calcified glioma of the right temporal lobe was made, luminal was prescribed, and the patient was kept under observation.

In June, 1934, the patient developed neuralgic pains in the right side of the face. The headaches gradually became confined to the right forehead and temple, but he averred that they were not nearly so frequent, nor did they last so long. He was found to have papillœdema of 1·5 D. Fresh radiograms of the skull showed a striking contrast with the earlier ones: there were now marked indications of increased intracranial pressure—thinning of the temporal squame on the right side, erosion of the sella turcica and increase in the diploë; the area of pathological calcification in the right temporal lobe had grown considerably in size. Operation was performed, and a large oligodendroglioma removed from the right temporal lobe.

It is incredible that the headaches from which this patient suffered could have been due to pressure on the dura mater. They antedated other symptoms by a period of several years, and were proved by an encephalogram to be unassociated at that time with any hydrocephalus. During the nineteen months before operation, the pressure on the dura mata was slowly increasing, as evidenced by the incontrovertible radiographic signs and by the terminal development of papillœdema; yet this headache gradually improved! The neuralgic pains in the right side of the face, although unassociated with any demonstrable loss of cutaneous sensibility, may have been due to pressure upon the Gasserian ganglion, or possibly they were referred from the dura mater of the middle cranial fossa.

A patient, aged 27 years, had suffered for two years from occipital headaches which radiated into the neck. A suboccipital decompression was performed, but the dura mater was not opened. This operation gave relief from headache for six months. Symptoms then recurred, and at a second operation a cerebellar ependymoma was removed. Although left intact at the first operation, the dura mater had gradually become stretched during the interval between the operations, so that a considerable cerebellar hernia developed.

In this case, when the dura mater was left unsupported by bone, the intracranial pressure was sufficiently high to stretch it, yet headache was relieved for a considerable time. If the dura mater were the sensitive structure responsible for headache, one would have expected that with its progressive stretching, headache would have been a conspicuous feature.

Unilateral headache cannot be adequately explained on a basis of dural

stimulation by pressure. The differences in pressure within various parts of the brain when a tumour is present must be very small indeed, for the brain being so soft, is immediately displaced from an area of high pressure to one of low pressure; proof of such displacement is found at post-mortem. The following case illustrates clearly the difficulty of accepting the dura mater as the sensitive structure.

A patient had an operation for a glioma of the right frontal lobe, which subsequently recurred. The headache of which she complained was paroxysmal in type and affected only the right side of the forehead. A large cystic cavity was located in the right frontal lobe, from which yellow fluid under a low pressure could be aspirated in quantities up to three ounces; this procedure usually gave relief from headaches after a few days had elapsed. A second operation was eventually performed, when the cavity was explored and a considerable amount of tumour which was lining the anterior part of the cavity was removed. Posteriorly the cyst came into contact with the right ventricle, a septum of paper thinness separating their contents; this septum measured about 3 by 2 cm. The aim of the operation in this case was to drain the contents of the cyst into the ventricle in order to obviate repeated aspiration, and to achieve this the septum was freely opened.

The unilateral headache in this case could not have been caused by local pressure on the dura mater. Not only was the pressure within the cyst never observed to be greater than 70 mm. during a headache, but any increase of the pressure of its contents would be communicated immediately and completely to the ventricle. In this manner, the ventricular system would be maintained at the same hydrostatic pressure as the cyst. It is notable that the operation did not give the patient immediate relief from the pain, confirming the view adopted. Headache slowly subsided during the course of the succeeding few weeks.

Headache from causes other than brain tumour.

Consideration of certain conditions other than intracranial tumour suggests the possibility that headache may be vascular in origin. Patients suffering from an intracranial aneurysm often complain of recurrent headache, which commonly affects one side of the forehead more than the other. In fact, it is taught that periodic unilateral headache, which never changes from one side to the other, is more likely to be due to an aneurysm than to be migrainous. The sudden severe pain which heralds a subarachnoid hæmorrhage may be felt in or over one eye—and at the post-mortem examination the aneurysm is found in the same side of the head. This suggests that the gradual stretching of the wall of the artery and the final rupture of the aneurysm may set up a train of afferent stimuli which is interpreted as headache. The aneurysms which develop from the circle of Willis are not of sufficient size to cause an increase in the

intracranial pressure. The large ones which occasionally develop from the internal carotid artery usually cause no headache, but give rise to pain in the face owing to pressure upon the neighbouring branches of the Gasserian ganglion.

In the following case it is difficult to avoid the supposition that the headache was of vascular origin, and that the interference with the blood flow consequent upon carotid ligation provoked afferent stimuli similar to those provoked by the aneurysm.

A woman, aged 41 years, suffered from right frontal headaches, and developed a right oculo-motor palsy. The diagnosis of aneurysm of the right posterior communicating artery was confirmed by arteriography, and the right internal carotid artery was ligated in the neck. Half an hour after the operation, the patient developed a dull ache in the right side of the forehead, lasting for about twelve hours. She stated that this headache was similar to that which she had previously experienced ; it was easier sitting up, but was aggravated by lying flat ; histamine had no effect upon it.

Bramwell (1932-33) records a case in which the contrary observation was made: ligation of the internal carotid for an intracranial aneurysm banished the headache of which the patient complained, before the patient left the theatre.

Headache of varying degree and distribution frequently follows an epileptic seizure, whether or not there be a demonstrable organic lesion such as a tumour or an area of cortical atrophy. The headache may be severe and is clinically very similar to that which occurs with an intracranial tumour. The following cases have been chosen in order to illustrate these points.

A patient suffering from an astrocytoma of the right frontal lobe had had epileptiform fits for three and a half years. The fits were always followed by a right frontal headache. Eighteen months before admission to hospital, headaches occurred independently of the fits. These headaches were quite similar in situation and quality to the post-epileptic ones.

Another patient had suffered from bifrontal headaches for many years. For about one year before admission to hospital he had Jacksonian epilepsy, and each fit was followed by a headache similar to his former ones. At operation a spongioblastoma multiforme of the right frontal lobe was removed.

In two patients suffering from epilepsy, encephalography demonstrated an area of cortical atrophy. In each case the post-convulsion headaches only affected that side of the head in which this atrophy was present.

Cases such as these give support to a thesis which offers a common causal mechanism for the headaches of tumour and of epilepsy.

The Experimental Production of Headache.

I.—By Stimulating Intracranial Structures.

When the opportunity has presented, observations have been made during the course of operations under local anæsthesia to determine the sensitiveness or otherwise of the various tissues encountered.

(*a*) *Dura mater.*—It has long been considered that the greater part of the dura mater is insensitive to such operative trauma as cutting, clamping,

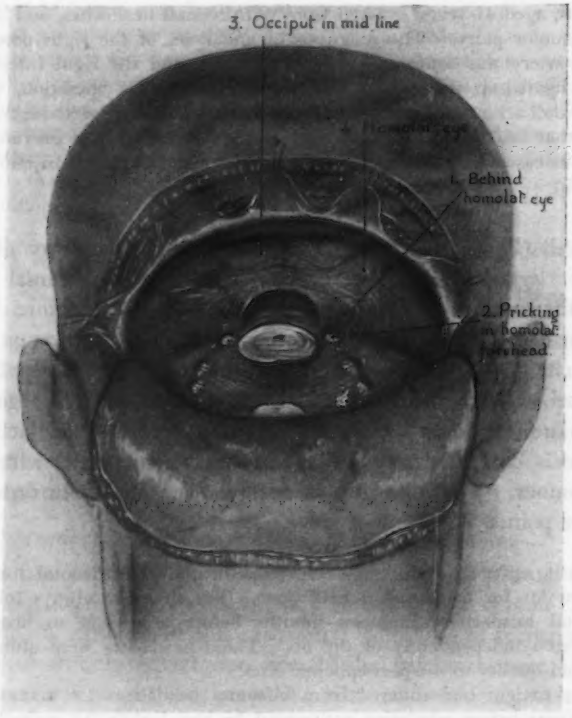

Fig. 1.

and burning, except in the immediate vicinity of the middle meningeal arteries, but the observations which follow show that this is not so.

During cerebellar explorations, I have inserted an instrument under the dura mater and exerted fairly heavy traction. In each of three cases, this gave rise to an ache at the back of the head on the same side, in one case radiating into the neck.

In four cases, the inferior surface of the tentorium has been stimulated by pressure with the tips of dissecting forceps (fig. 1). At a point (1) near its free edge, 2 cm. behind the right trigeminal nerve, pain was experienced behind the right eye, somewhat less severe than the pricking pain which was felt in the forehead when the trigeminal nerve itself was touched (2). Pressure and traction (3) during the removal of a tumour caused pain

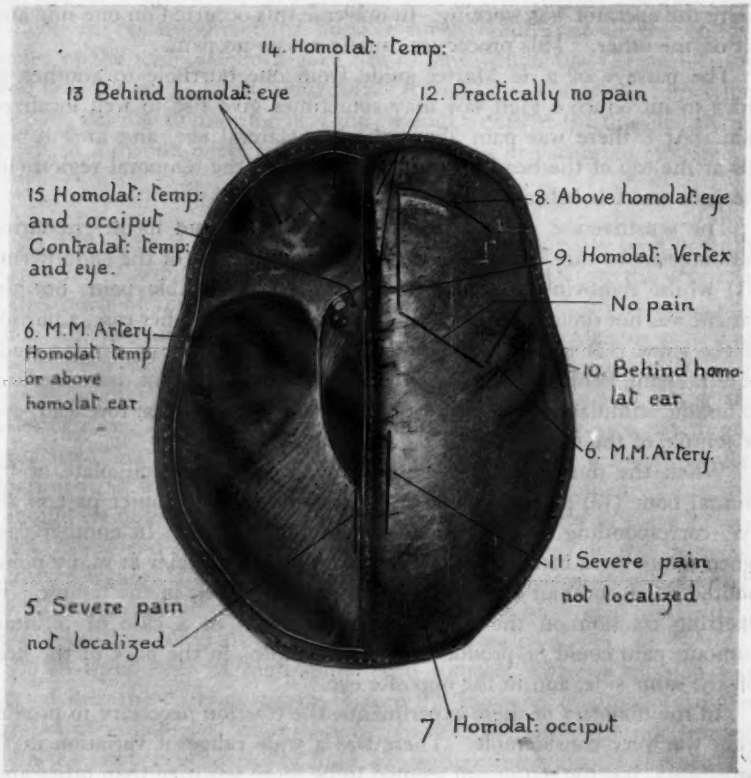
14. Homolat: temp:
13 Behind homolat: eye
12. Practically no pain
15 Homolat: temp: and occiput Contralat: temp: and eye.
8. Above homolat: eye
9. Homolat: Vertex
No pain
6. M.M. Artery Homolat temp or above homolat ear
10. Behind homolat ear
6. M.M. Artery.
11 Severe pain not localized
5. Severe pain not localized
7 Homolat: occiput

FIG. 2.

in the middle of the back of the head, none in the eyes. The touch of the forceps (4) in another case caused the patient to complain of pain in the homolateral eye. When the endothermy was applied to the upper surface of the tentorium in the middle line (5) (fig. 2), or when traction was exerted on it, the patient complained bitterly of pain, but he was too unco-operative to describe its location.

Stimulation of the middle meningeal arteries (6) either by clamping or by endothermy results usually in a fairly acute pain, referred to the homolateral side of the head, either in the temple or just above the ear. On several occasions this manœuvre has been painless.

While drilling a hole for ventriculography, in two cases there was pain in the back of the head when the dura mater in the parieto-occipital region (7) was stimulated by the perforator, the patient stating that it felt to be where the operator was working. In one case this occurred on one side and not on the other. This procedure usually causes no pain.

The passage of a de Martel guide from one burrhole to another in order to introduce a gigli saw may sometimes give rise to well localized pain. At 8 there was pain above the homolateral eye, and at 9 it was felt at the top of the head on the same side. In the temporal region (10) the pain was felt behind the homolateral ear.

The sensitiveness of the superior sagittal sinus and its neighbouring dura appears to vary considerably. In one case the use of the endothermy (11) whilst removing a meningioma caused considerable pain, but the patient was not sufficiently helpful to localize it. In another case, a portion of the sinus (12) was removed practically painlessly. In a similar study of dural pain, Penfield (1935) has frequently found this sinus quite sensitive to faradic stimulation, the pain being referred to the vertex, forehead, eye, or temple of the same side.

When the dura mater is being stripped off the orbital plate of the frontal bone (13) pain may be felt behind the inner or outer part of the eye, corresponding to the area of dura mater affected. In another case, when removing a meningioma, traction on the dura mater at many points behind the frontal air sinus (14) caused pain to be felt in the temple. By exerting traction on the diaphragma sellæ (15) in a case of pituitary tumour, pain could be produced in both temples, in the back of the head on the same side, and in the opposite eye.

In the majority of these experiments, the traction necessary to produce pain was very considerable. There was a wide range of variation in the sensibility, but the tentorium seemed to be more sensitive than other areas of the dura mater, excepting that around the middle meningeal vessels, and the dura mater lining the vault the least sensitive.

(*b*) *Cerebral arteries.*—In five patients, observations have been made on the effect of pressing upon, or displacing the internal carotid artery in the vicinity of the anterior clinoid process. In two, pain was appreciated behind or in the homolateral eye, in one the pain was referred to the temple on the same side, and in another pain was experienced in the region of the

homolateral eye, not satisfactorily located, when arachnoidal adhesions were being divided close to the internal carotid artery. No sensation was experienced in the fifth case.

(*c*) *Brain tissue and walls of ventricles.*—In no case did sensation of any kind result from pressure upon the pia mater, the brain tissue or upon the walls of the ventricles. The cortical veins and arteries and the choroid plexuses were insensitive to clamping and to endothermy. In two cases, traction in certain directions upon a tumour adherent to the choroid plexus of the temporal horn gave rise to pain which was felt deep in the head near the vertex on the same side. It could not be ascertained whether the pain was due to movement of the choroid plexus or the middle cerebral artery, or a distant effect on the cavernous sinus or Gasserian ganglion.

II.—By Altering the Intracranial Pressure.

(1) The effect of raising the intraventricular pressure has been noted in four cases. Warm Ringer's solution was quickly injected into the ventricles in the course of ventriculography, before the removal of any cerebrospinal fluid. In two cases no headache occurred. In a third case this caused an exacerbation of occipital headache which was already present. It is interesting that in this patient, traction on the dura mater lining the posterior fossa, in the manner already described, did *not* give rise to any headache. Contralateral frontal headache resulted from a fourth similar experiment, in which the intraventricular pressure was suddenly increased. It should be noted that injecting fluid into the ventricles in these experiments raised the general intracranial pressure, as well as the intraventricular pressure. Consequently its effect may not necessarily have been due to distension of the ventricle. In fact, we have seen that direct pressure on the wall of the ventricle does not cause pain.

(2) In three cases of high spinal cord tumour, Ringer's solution was injected into the cisterna magna, before the injection of lipiodol for the purposes of radiological examination. In one case, after the injection of only a few cubic centimetres of fluid, the patient immediately complained of headache affecting the front half of the head. The headache rapidly subsided as the fluid was withdrawn. In the other two cases, the injection of 10 c.c. of fluid had no such effect.

(3) Before opening the dura mater in the course of a cerebellar exploration, I have observed that 20 c.c. of Ringer's fluid injected under the dura mater, probably into the subdural space, has resulted in homolateral occipital headache, which gradually disappears as the fluid escapes. It is usual in posterior fossa operations, to relieve the intracranial tension by

tapping an occipital horn, so that the dura mater may be opened with the least risk of damaging the brain, and the escape of ventricular fluid may be aided by gentle pressure upon the dura mater. This has on occasion been accompanied by occipital headache, although the fluid escapes freely through the needle. In one case when the gentle pressure on the cerebellar region was removed, the pain suddenly became *more acute* for a few seconds.

(4) Compression of the jugular veins for two minutes induced headache in six out of nine cases, and in four of these, the resting intracranial pressure was not above 200 mm.

(5) In many cases headache was produced by suddenly *reducing* the intracranial pressure. One of the patients in whom jugular compression produced headache, stated that the headache became much *worse* as the compression was removed. A subdural hæmatoma was subsequently found over the right hemisphere: it is noteworthy that the experimental headache was quite similar to his usual headache, being situated in the right side of the forehead.

(6) In five cases, when the lateral ventricle was tapped, the sudden escape of fluid was attended by considerable pain. On one occasion the intraventricular pressure was 550 mm., the patient being seated, and bifrontal headache occurred when the pressure fell below zero. On disconnecting the manometer, air hissed into the ventricles, and the headache completely subsided. In another patient with a frontal glioma, the pressure at ventriculography was 270 mm. When the ventricle was tapped on account of headache during the operation an hour or so later, the pressure was zero and the headache was relieved by pressing on the dura mater.

(7) The sudden release of fluid pent up in an arachnoid cistern has been noted twice to give rise to headache. When defining the lateral margin of a large suprasellar meningioma near the anterior clinoid process and the internal carotid artery, there was a sudden gush of cerebrospinal fluid from the cisterna chiasmaticus. As the fluid escaped, the patient complained of prolonged and severe aching in and over both eyes. In another case the puncture and sudden release of fluid from a much distended cisterna magna caused headache, so intense, that the patient was unable to state where it was.

(8) To illustrate the production of headache by decreasing the intracranial pressure, I will describe details of experiments upon a man who had an enormous cystic tumour of the anterior half of the right cerebral hemisphere. Many years previously a right subtemporal decompression had been performed with relief of his symptoms for a long period. A mano-

meter was connected to a needle in the cyst, and another to a needle in the opposite left ventricle. The initial pressure on each side was the same, 195 mm. After 25 c.c. of cerebrospinal fluid had escaped from the left ventricle, the pressure was 120 mm. each side, and headache gradually developed. With each further decrease in the pressure as fluid escaped from the ventricle, there was an exacerbation of the headache, but pressure upon the decompression gave complete relief. When the pressure fell as low as 10 to 40 mm. the headache, which was fairly severe all over the forehead and in the decompression, was made much worse by pressing on the decompression. At this stage, tilting the table so that the head was lowered increased the pain, and jugular compression and the intravenous injection of histamine also made the headache worse. The headache now remained fairly constant in intensity, and taking further fluid out of the ventricle or putting some back did not influence it. Although this headache was clearly induced by reducing the intracranial pressure, it could not be relieved by reconstituting the normal pressure, but subsided spontaneously in a few hours. This suggests that a change occurred in the sensitive tissue concerned, which was not immediately reversible.

III.—Combined Ventriculography and Encephalography.

It has always appeared to me as a significant fact that the procedure of ventriculography is usually associated with little or no discomfort, yet encephalography is intensely painful. When air is injected into the lumbar theca in the sitting position, headache usually commences after the replacement of about 20 c.c. of fluid, and is felt first in the occipital region, spreading subsequently to the vertex and forehead. Jugular compression provides some relief from the pain, more especially in the earlier stages than later when most of the cerebrospinal fluid has been removed. The pain is bilateral, but if the air be injected with the patient in the lateral position, then headache develops only in that side of the head lying uppermost. On sitting up, the pain becomes much more severe and spreads to both sides of the head equally. Penfield (1927) has made similar observations, and has proved radiologically that the air passes to any desired part of the vault with the production of a headache on that side.

I shall now describe an experiment combining ventriculography and encephalography. The usual parietal burr holes were made, and with the patient seated, a needle was inserted into the lumbar theca; its stylet was not yet removed, so that fluid should not escape. The ventricles were tapped and the fluid contents replaced by air without any discomfort. With the needles still in position so that there was a free communication

between the ventricles and the external air, lumbar insufflation of air was now performed. After some 20 c.c. of fluid had been replaced by air the usual headache developed. The experiment was repeated in another patient with precisely similar results.

Since headache does not occur in ventriculography when usually little or no air enters the subarachnoid spaces, and since headache *does* develop in encephalography with the ventricles kept at normal atmospheric pressure, one may conclude that in these circumstances the responsible sensitive structure is not within the ventricle. The sensitive mechanism must be related to the dura mater with its vessels and sinuses, or the pia-arachnoid membranes and enclosed vessels, provided one assumes that the brain tissue itself is insensitive.

From the study of clinical material it has already been demonstrated that the absolute value of the intracranial pressure bears no constant relation to the presence or absence of headache. On the other hand the experimental observations recorded in this section clearly indicate that the sudden increase or decrease of a pressure previously normal or abnormal readily causes headache. A rapid reduction of the pressure is perhaps the more conspicuously successful method. The conclusion may therefore be drawn that *it is the sudden variation in the intracranial pressure which induces experimental headache, not the steady pressure itself.*

IV.—Collapse of the Brain.

A most unusual and dramatic cause for pain was observed in five patients with colloid cysts of the 3rd ventricle or basal ganglia tumours, in each of whom ventriculography had demonstrated grossly dilated ventricles. The ventriculography was performed immediately before operation and as much fluid as could be obtained was replaced by air with insignificant discomfort. In order to expose the tumour a piece of brain was excised so that a wide opening was made into the ventricle. When the air which was gently distending the ventricle suddenly escaped, the whole hemisphere collapsed like a punctured balloon. This sudden collapse of the brain was associated in each case with an immediate intense pain in the head. The precise distribution of the headache was not determined, and it disappeared after a few minutes. The significance of these observations will be discussed later.

V.—Headache Produced by Histamine.

Pickering and Hess (1933-34) were the first to make a detailed study of the headache which results from the intravenous injection of histamine

acid phosphate. Their valuable contribution has been entirely confirmed by many other workers. The intravenous injection of 0·1 mgm. of histamine in normal subjects usually produces a bifrontal throbbing headache which develops about forty-five to sixty seconds after the injection, and subsides in the course of five to ten minutes. Histamine is a vasodilator, and consequently within a few seconds of its injection the systemic blood-pressure falls, and the cerebral vasodilatation causes the cerebrospinal fluid pressure to rise, by reason of the increase in the volume of the brain and its cortical vessels. In their experiments Pickering and Hess found that the headache developed when these changes were subsiding; in particular when the cerebrospinal fluid pressure was falling, and the blood-pressure was rising to normal. Moreover they showed that the headache might be relieved either by raising the intracranial pressure, or by lowering the blood-pressure. Clearly, the headache produced in this manner cannot be due to a rise in the intracranial pressure.

In order to compare the headaches of intracranial tumour with that produced by histamine, I have injected histamine into fourteen patients suffering from tumour. In three no headache occurred, and in normal persons histamine does not invariably cause headache. In each of the remaining eleven patients, the headache which occurred was similar in quality and distribution to that produced by their tumour. If the headache due to the tumour presented peculiar features, such as restriction to one side, then the headache from histamine had the same characteristics. One case illustrates this most conspicuously. The spontaneous headache for which the patient sought admission to hospital was an intense pain over the right side of the forehead, spreading up to the vertex, and as the headache developed, so the whole side of the forehead broke out into profuse sweating. Histamine produced an identical headache and sweating.

It was not possible to check these studies by measuring the pressure of the cerebrospinal fluid, but the changes in the blood-pressure were recorded, and it was found that the headaches always began as the blood-pressure was returning to normal. Clearly, in subjects suffering from a tumour, as in normal subjects, the headache produced by histamine cannot be due to the rise in intracranial pressure.

I have endeavoured to determine whether histamine causes headache by virtue of its effect on the vessels of the dura mater, or on the cerebral vessels. The minor operation of cerebral arteriography performed under local anæsthesia has presented this opportunity, and in thirteen patients I have injected histamine into the carotid arteries. Three of the patients

experienced no headache at all. In the remaining patients, histamine was injected fifteen times into the common carotid artery, and headache resulted every time at intervals of from three to sixty seconds after the injection (Chart 4). Six of the headaches were confined to the side of the

CHART 4.

THE EFFECTS OF INJECTING HISTAMINE INTO THE CAROTID ARTERIES.

15 injections into the common carotid artery:
- in 6 cases, headache was entirely homolateral.
- in 9 cases, headache was worse on homolateral sides, or equal each side.

6 injections into the internal carotid artery:
- in 5 cases, headache was homolateral. (becoming slowly generalized in one case).
- in 1 case, headache was absent.

6 injections into the external carotid artery:
- in 5 cases, headache was entirely absent.
- in 1 case, faint generalized headache occurred.

injection, and the remaining nine were either bilateral or developed earlier on the homolateral side and affected it much more than the contralateral side. On six occasions the injections were made consecutively into the internal and external carotid arteries of the same side. On five occasions, injection into the internal carotid artery was followed by homolateral headache, which in one case very slowly became generalized. In these same patients, however, *no* headache at all was produced by injecting the histamine into the external carotid artery. The sixth case was unusual, for injection into the internal carotid artery did not cause headache, but a very faint generalized headache slowly developed thirty seconds after the external carotid was injected.

The middle meningeal vessels are divided during the course of many intracranial operations, either at the foramen spinosum, or at the junction of the floor and the lateral wall of the middle cranial fossa. Histamine was injected intravenously into several patients who had had such an operation, and headache was felt on both sides of the head.

Several conclusions may be drawn from these experiments. The rapidity with which some of the headaches developed and their restriction to the side of the injection suggest that this experimental headache depends primarily on an alteration in *calibre* of the intracranial blood-vessels. Furthermore, there is strong evidence that the vessels affected are the cerebral vessels, branches of the internal carotid artery, and not the meningeal vessels of the dura mater derived ultimately from the external carotid artery.

The Effects of Sympathectomy and of Trigeminal Nerve Root Section on Histamine Headache.

Pickering and Hess stated that the removal of the stellate sympathetic ganglion did not abolish histamine headache. I have confirmed this in four cases. They noted, however, that the headache did not develop on the side of operation in patients in whom the trigeminal nerve had been divided. I observed the effect of histamine injection in seven such cases in whom the sensory root of the trigeminal nerve had been completely divided. In three cases, my observations confirmed those of Pickering, for headache was restricted to the forehead and temple of the normal side. In one of these patients, the headache also affected the back of the head, equally on both sides. In two other cases, however, the headache was equally distributed over both sides of the head, one of the patients stating spontaneously that the pain was worse on the side of the operation. In the two remaining cases, the injection of histamine did not give rise to any headache. One of these subjects was willing to co-operate further, so I injected 10 c.c. of air into the lumbar theca while he was in the sitting position. Headache developed at first in both sides of the back of the head, and later affected the forehead and temple of the normal side only.

Observations on the Relief of Headache.

The relief of headache has been studied but with less successful results, for the provocation of a headache by experimental methods has been effected far more readily than its relief. Raising or lowering the head of the bed has occasionally given relief, but either position has been found helpful in cases of high intracranial pressure. If the headache was associated with an abnormally low pressure, elevating the foot of the bed usually abolished it. There has been no convincing evidence that amyl nitrate, histamine, or ergotamine tartrate had any consistent effect on the headache.

The intravenous injection of a hypertonic solution of sodium chloride or glucose has at times given considerable relief. The following two cases are good examples.

(1) A boy, aged 16, had experienced headaches and vomiting for three weeks before admission to hospital. The headaches were bifrontal and paroxysmal in type, associated with pain and stiffness of the neck. An operation was performed for the removal of a cerebellar angioma which had bled, causing acute hydrocephalus. Prior to the operation, the headache became so intense that he was given 40 c.c. of a 15 per cent. solution of sodium chloride. Relief was afforded almost immediately, and he said he felt better than at any time during the preceding few days.

(2) A woman, aged 30, had had paroxysms of agonising headache for three weeks before admission to a nursing home. Although drowsy, the recurring headaches were so severe that she had not slept for four successive nights. Following the intravenous injection of 80 c.c. of a 50 per cent. solution of glucose, the headache was greatly relieved, and the patient was able to sleep. At operation next day a colloid cyst of the third ventricle was removed.

A moderately severe headache was immediately relieved by tapping the ventricles, the tension being considerably above normal. Three times, partial relief was occasioned by tapping a cystic tumour. One of these was a recurrent cystic glioma of the frontal lobe, and the pressure of the cystic fluid was only 70 mm. The headache was somewhat relieved as fluid dripped from the needle, but if vigorous aspiration were attempted, the headache immediately became worse.

I am indebted to Professor Paterson Ross for the opportunity of studying a patient who had had a successful subtemporal decompression many years ago for symptoms of a cerebral tumour. He sought readmission to hospital on account of symptoms suggestive of a recurrence of the tumour. As part of the investigation which subsequently excluded the likelihood of a tumour, a lumbar puncture was performed. A day or so later, every time the patient sat or stood up, the decompression became deeply concave, and he experienced intense contralateral frontal headache. The headache subsided when he lay down, and the decompression became less concave. This condition persisted several days, until 50 c.c. of warm saline were slowly injected into the lumbar theca when the patient was in the lateral position. The decompression now bulged and when he sat up, the headache no longer occurred. He remained practically free from headache without any further injections of fluid.

Discussion.

The observations presented in this paper, and those published by others, afford incontrovertible evidence that certain areas of the dura mater possess considerable sensitiveness when suitably stimulated, and it has been almost universally accepted that the dura mater and its vessels are the sensitive structures responsible for the production of headache. From the clinical observations recorded in this paper it is clear that an explanation which is based upon dural sensibility is inadequate. Many speculations have been advanced to explain precisely how the dura responds, and I will indicate further difficulties which prevent an acceptance of them.

Dural sensibility as tested at operation depends upon a fairly severe pressure, which if prolonged, would probably result in tissue ischæmia. The pain which results is usually fairly sharp and confined to a small area,

the position of which the patient can locate with fair accuracy, but the difficulty in finding a suitable description for spontaneous headaches is common experience, and their location is usually vague. An example of this is offered in cases of tumour of the cerebellum adherent to the tentorium. Pain is rarely felt in the eyes, though this is the characteristic result of stimulating the tentorium. Moreover, dural pain ceases shortly after the stimulus is removed, but altering the intracranial pressure causes headache which frequently persists for several hours, in spite of the restitution of the normal pressure. The suggestion has already been made that this signifies some change in the sensitive tissue which is only slowly reversible, and cannot be a simple pressure effect upon the dura mater.

How can a tumour so stimulate the dura mater as to produce frequently recurring paroxysms of headache, the intervening periods being free from pain? If it is merely an increase of intracranial pressure which stimulates the dura mater, why does not headache regularly occur in normal people when jugular compression is performed, or each time one coughs violently? There are many who will maintain that this fails to excite headache because it increases the pressure uniformly within the skull. They consider the stimulus to arise from unequal pressures on the sides of the tentorium or falx. But every morning on rising the brain must weigh more heavily on the tentorium, with no ill-effects. One may press on a subtemporal or cerebellar decompression almost to the point of damaging the brain, yet apart from slight discomfort the patient denies any real headache. If the dura mater were the responsible structure, one would expect the pain to be more frequently referred to areas supplied by the Gasserian ganglion. Such associated pains in the face do occasionally occur, as distinct from so-called false localizing signs due to direct pressure upon the ganglion. They are met with more frequently amongst patients with a pituitary tumour, and I believe, in those cases in which a tumour gains a secondary attachment to the dura mater, such as occurs with a cerebral abscess. That headache occurs in cases of pituitary tumour is considered to be strong evidence that pressure on the dura mater causes headaches, by reason of the confined dural limits in which this tumour grows. It seems very probable that more than one mechanism may be operating in these cases. The poorly-localized, dull bifrontal headaches may be caused in the same manner as in other intracranial tumours, whereas the radiating neuralgic facial pains may well be referred from the dura mater.

The headache due to histamine cannot be explained by dural stimulation. It occurs only with a falling intracranial pressure, and is relieved

either by increasing or by lowering the blood-pressure, and I have already shown that the middle meningeal vessels are not responsible.

This question of the dural origin of headache must now be finally answered, before passing to the constructive portion of the discussion. It is conceded that direct stimulation of the dura mater by direct pressure, or by its involvement in the disease, may occasionally be the cause of headaches. Such headaches are of a special neuralgic type; they usually occur in cases of pituitary tumour and only rarely in cases of tumour elsewhere in the cranium. But from the available clinical experimental evidence the conclusion is inescapable that the dura mater is not the sensitive structure which is responsible for the common headaches of intracranial tumour.

* * * *

The only intracranial tissue other than the dura mater which is sensitive to suitable stimuli is apparently the cerebral blood-vessels. That headache might be vascular in origin has already been suggested, and this aspect of the subject will now be discussed. I shall proceed to indicate in what way the vascular changes which occur during histamine headache may be related to the statement that "it is the sudden variation in intracranial pressure which induces experimental headache." A proposition in explanation of headache will follow further elaboration of the argument.

Let us consider the forces within the cranium which may influence the calibre of the smaller cerebral arteries. There are three variants: the intravascular pressure of blood distending the vessel wall, the tone of the vascular musculature, and the intracranial pressure which supports the outer surface of the vessel—this may be termed the extravascular pressure. Since these forces act within a semi-rigid container, the variation of one beyond certain limits must influence the others to some degree. Histamine injected intravenously causes generalized vasodilatation; the blood-pressure, and therefore the cerebral intravascular pressure falls, and because of the increase in calibre of the cerebral arteries the intracranial (extravascular) pressure passively rises. As the effect of the drug subsides, the tone of the systemic arteries recovers more rapidly than that of the cerebral arteries, so that the tone of the cerebral vessels is still less than normal when the intravascular pressure has regained its former value. It is at this point that headache is appreciated. Clearly, as Pickering and Hess pointed out, during this period of lag in the return of vascular tone, the walls of the cerebral vessels are being subjected to an unusual degree of tension, and they suggested that it was this abnormal state of tension

which gave rise to the headache. The relief obtained by increasing the intracranial pressure and consequently giving greater support to the vessel walls, and the relief which resulted from diminishing the blood-pressure and the distending effect of the intravascular pressure, is evidence which strongly supported this view. When histamine was injected intravenously into a patient with a recurrent right frontal glioma, in whom an enormous cerebral hernia had developed through a wide bone defect, the headache was more severe on the right side of the head. This may be explained by the lack of external support to the vessels of the right frontal lobe which the intact skull would have afforded.

Clark, Hough, and Wolff (1935) have performed experiments which still further favour this explanation of an abnormal state of tension in the walls of the cerebral blood-vessels. Simultaneous photographic records were made of the pulsations of the temporal artery, and of the cerebral vessels as reflected in the pulsations of the cerebrospinal fluid. The increase in the excursion of each pulsation was very much greater in the cerebral vessels than in the temporal artery, during the period when histamine headache was experienced.

Since the intravascular pressure is opposed by the extravascular pressure and by the tone of the vessel wall, any sudden drop in the extravascular pressure—as occurs when the ventricle is tapped—would cause a relative degree of abnormal stretching of the vessel wall, unless the tone of the muscle were immediately adjusted. Such an experimental procedure was found to be very successful in provoking headache, and that it may be due to a change in vascular tension is an hypothesis comparable with that given for histamine headache. Whether it is the adventitia or the media, or both, which respond to the stimulus is not clear.

Can the headaches due to an intracranial tumour, or due to an experimental rise in the intracranial pressure, be explained upon a similar basis? In order to answer this question, the behaviour of the cerebral circulation in the presence of an intracranial tumour must be briefly considered.

In order to maintain an adequate blood supply to the brain, a delicate balance is maintained between the lumen of the smaller cerebral arteries and the velocity of the blood flow. The velocity of the flow of blood through the cerebral vessels depends upon the relation between the intracranial venous pressure and the intracranial arterial pressure. According to Wolff and Blumgart (1929) when the intracranial pressure is raised a slowing of the blood-flow occurs. In consequence of this, cerebral veins, capillaries, and arteries dilate in order that the blood supply may be adequately maintained. The slowly growing tumour gradually compresses

the brain in order to acquire room and in so doing imperils the blood supply; this necessitates some degree of vasodilatation and consequently there is an increase of pressure within the capillaries. It is this progressive vasodilatation which results in the rise in intracranial pressure in the course of the disease. When the cerebrospinal fluid pressure is measured, one obtains an index of the cerebral capillary pressure, and the venous pressure is closely related. An increase of intracranial pressure in disease indicates primarily an increase of the pressure within the arterioles and capillaries. It is no measure of the bulk of the tumour, for at post-mortem the pressure is zero. This is in accord with clinical experience, for the intracranial pressure may be normal in a patient with a very large meningioma, or in one with a condition such as a colloid cyst of the third ventricle which has nevertheless produced conspicuous dilatation of the ventricles. So slow is the growth of the tumour that the brain adapts itself by gradual displacement, compression, and even atrophy. The process is too slow to affect the general intracranial circulation until the terminal stages when the limits of compensation have been reached, and although it is quite evident that the disease has been present for a long time, only a relatively short history of recent headache may be obtained. On the other hand, a more rapidly growing tumour such as a glioma, although it may be small, will readily cause progressive disturbance in the cerebral circulation, resulting in a raised intracranial pressure and liability to headaches. In order to maintain an adequate blood flow fluctuations must occur in the tone of the vessel walls, and consequently in the intravascular and extravascular pressures. In this relatively labile state, conditions are highly favourable to the disturbance of proper balance between these three variants. Such a lack of balance will subject the vessel wall to an abnormal strain. The view is therefore advanced that *the headache in intracranial tumour is due to some disturbance of the tension of the walls of the cerebral vessels.* It is this disturbance of tension which provides the adequate stimulus for the excitation of pain.

Many clinical observations give direct support to this explanation of headache. Attention has already been drawn to the similarity between the headache produced by histamine and that due to a tumour. This similarity is remarkable since histamine evokes the peculiarities of certain tumour headaches, and indicates that one and the same sensory structure is being stimulated. The pain which occurs during operations when the brain collapses may be deemed vascular in origin, being due to the sudden gross distortion of the arterial tree. An alternative explanation might be offered in these cases, and for the headache of encephalography. Con-

siderable traction must be exerted upon the veins entering the great sinuses as the brain falls away from the dura mater, and this traction may stimulate the sinuses. This however implies a dural origin for the headaches and such can no longer be admitted. Moreover, the pain of collapse of the brain was momentary although the tension upon the veins was maintained. The headache of encephalography endures for some hours and is but slightly relieved in the recumbent position, in which position most of the veins will be relaxed. The unilateral headache which follows the intrathecal injection of a small quantity of air when the patient is lying in the lateral position may be due to a local difference in the support afforded the cortical vessels.

The clinical evidence that in the majority of cases the tumour is situated on the same side as the unilateral headache, suggests that the headache depends upon some local feature, and some abnormality of vessel tension forms an adequate basis for explanation. The walls of vessels in the immediate vicinity of a tumour may well be in a different state of tension from those more distantly placed. Such strain may be dictated by some local vasomotor influence. A similar state was produced experimentally when histamine was injected into the carotid artery and caused homolateral headache. Paroxysmal headaches can also be satisfactorily explained in this way ; the variation of intensity in the headache may originate in some vascular crisis which has arisen in order to maintain an adequate blood flow. These crises will naturally become more severe during the closing phases of the illness, corresponding with the progressive intensity of the headaches. The frequent termination of these headaches in unconsciousness and in an epileptiform convulsion makes such an explanation reasonable.

Headache is frequently of minimal degree in elderly patients suffering from spongioblastoma multiforme. Not only may it be entirely absent, but the intracranial pressure is often normal, although at autopsy the tumour proves to be of considerable magnitude. This type of glioma is very malignant, and in spite of its rapid increase in size, the surrounding brain becomes extensively infiltrated rather than compressed. In this way the joint bulk of the tumour and the brain may not be much increased, and the cerebral circulation is not hampered. In a personal communication, Dr. J. G. Greenfield suggests an alternative explanation. In elderly persons the subarachnoid spaces are frequently very capacious and consequently accommodation is provided for a considerable growth of a tumour without an undue rise in the intracranial pressure.

Gibbs (1934) analysed the frequency of the various symptoms produced

by tumours in different parts of the brain. He found that the curve of the incidence of severe headaches followed that of the incidence of generalized convulsions more closely than the curve of any other symptom. This observation is of interest when considered with the cases previously quoted, which demonstrated the similarity between the headaches due to a tumour and those due to an epileptiform seizure. The latter headaches may very likely have a vascular origin, for there is general agreement that during convulsions widespread changes occur in the diameter of the pial arteries, although the significance of these changes is not yet appreciated. Penfield (1933-34) states that the typical vasomotor phenomena consist of an arrest of visible pulsation in the arteries during the seizure, followed by a period when the vessels pulsate more violently and more rapidly, and the veins may assume the hue of arteries. Except for the cessation of pulsation, this description accurately resembles the appearance of the exposed brain after the patient has received an intravenous injection of histamine during the course of an intracranial operation. Furthermore, it is during this period of excessive pulsation that histamine headache is appreciated. It may be asked why many epileptics do not experience headache. The explanation probably lies in the degree of the vascular distortion. In their experiments, to which reference has already been made, Clark, Hough and Wolff concluded that the "threshold" for headache varied widely in different subjects. Of paramount importance was their observation that *"in a given individual after a vasodilator agent (histamine) which caused headache, the distortion of the vessels was nearly twice that following another vasodilating agent (carbon dioxide) which caused none."*

There are several serious objections to this suggestion of a vascular origin of headache which must be answered. The most obvious and the most difficult to refute is based on anatomy. Along what pathways are the afferent stimuli conducted, and what course do the nerve fibres take in order to reach the brain? It is known that no afferent fibres descend from the superior cervical sympathetic ganglion, nor does stellate ganglionectomy prevent headaches. Furthermore it has been shown that total section of the sensory root of the trigeminal nerve abolishes headache, though not invariably. This evidence has hitherto only been interpreted as indicating that the meningeal vessels are the structures responsible for headache, and these have already been excluded. But it may be asked whether any branches pass from the Gasserian ganglion or from its sensory root, to join the carotid plexus and perhaps serve as an afferent pathway from the cerebral vessels. There is no evidence on this very important detail of anatomy. Stöhr (1928) only considers it, without com-

mitting himself; Dowgjallo (1929) states that branches pass from the trigeminal nerve to the carotid plexus, but gives no supporting evidence. In a personal communication, Professor Donal Sheehan informs me that he has made careful dissections of eight specimens of the cavernous sinus. In every specimen, he has found several connections between the Gasserian ganglion and the sympathetic plexus around the carotid artery. He points out, however, that from dissections alone, he is not prepared to say whether these connections convey sympathetic fibres to the 5th cranial nerve, or sensory fibres from the carotid artery.

There are some suggestive experiments which help to fill this hiatus in anatomy. Davies and Pollock (1932) found that reactions of pain were produced in animals when a stimulus was applied to the superior cervical ganglion, after all its branches had been severed except those fibres ascending into the skull on the internal carotid artery. These reactions were abolished when the trigeminal nerve and the upper posterior cervical roots on the same side were divided. They concluded that the pain was produced by some effect of the stimulus upon the structures innervated by the sympathetic nerves. This stimulus may well have set up an abnormal state of tension in the cerebral vessels, the afferent path for the pain being along the divided trigeminal and cervical nerves. This raises the question whether the vertebral arteries may not receive branches from the cervical nerves, in order to account for the occipital distribution of some headaches. Temple Fay (1931) has found that stimulation of the vertebral and basilar arteries causes pain in the back of the head and in the neck.

Similar conclusions may be drawn from the work of Penfield and Chorobski (1932), who have demonstrated that in monkeys, the vasodilator fibres to the cerebral vessels leave the brain by way of the facial nerve and gain the great vessels through the greater superficial petrosal nerve. Some of their experiments in nerve degeneration indicate that afferent fibres from the carotid plexus may join the geniculate ganglion and reach the brain through the nervus intermedius. They found that stimulating the distal end of the cut greater superficial petrosal nerve not only resulted in vasodilatation, but caused the animal to struggle when anæsthesia was light. This struggling was abolished when the trigeminal nerve was divided.

Levine and Wolff (1932) using galvanic skin responses as a criterion of pain, have made experiments on animals concerning the effects of stimulating electrically the blood-vessels and pia mater in various parts of the brain. They obtained results which indicated that afferent impulses were set up

most frequently and of greatest magnitude when the larger arteries were stimulated. In addition to my own clinical observations, other surgeons have reported cases in which pain resulted from stimulating the largest of the cerebral vessels, such as the middle cerebral artery. As these observers remark, negative results in man may only signify that the adequate stimulus was not being employed.

Objections may be raised against evidence which is based on a comparison of headache due to intracranial tumour with histamine headache. It has been noted that histamine headache is relieved by lowering the blood-pressure by the use of a vasodilator. Such treatment for the headache of intracranial tumour usually gives no clear-cut relief. The headaches associated with an abnormally low intracranial pressure are, however, relieved by artificially raising the pressure ; this action may well be similar to the relief which jugular compression affords histamine headache. It is not suggested, moreover, that headaches due to tumour are due to vaso-dilatation, but that an abnormal state of tension of the walls of vessels acts as the adequate stimulus. Drugs which are believed to act upon the cerebral vessels are unsuccessful when employed to relieve the headaches of tumour. In this connection, the considerable relief afforded by the intravenous injection of hypertonic solutions is of great significance. Although this procedure is known to reduce excessive intracranial pressure, it should not be assumed that the relief of the headache is necessarily a direct result of this reduction of pressure. Wolff and Forbes (1928) observed through skull windows the effect on the cortical circulation of the intravenous injection of hypertonic solutions. Following a transient vaso-dilatation (which could be prevented by injecting the solution very slowly) the pial arteries and veins gradually decreased in calibre, and this vasoconstriction was associated with a fall in the pressure of the cerebrospinal fluid and a rise in the systemic blood-pressure. The work of others is quoted, in which increase in the tone and in the peristalsis of the bowel, and pallor of the bowel wall and of the spleen due to vasoconstriction, were also observed following the intravenous injections of hypertonic solutions. These authors conclude that there is probably a direct action of these solutions on plain muscle. It is clear that these experiments offer considerable ground for the belief that the relief of headache by such methods is due to an immediate and direct effect upon the cerebral arteries, and consequently give further support to the proposition. Such an explanation fully accounts for the striking rapidity with which relief follows the injection, for this frequently occurs before the procedure terminates, or a few minutes later. Clearly, this is too soon for the effect to be due to the gradual fall

in the intracranial pressure which is effected by osmosis, though doubtless this delayed action prolongs the period of relief.

* * * *

I would like finally to put the headache of intracranial tumour into the perspective in which I view it in common with the disorders of the other great systems of the body. Abdominal pains may be considered to be either of somatic or of visceral origin, and Morley (1931) has emphasized the essential differences in character between these varieties of pain. Somatic pain has usually a sharp and stabbing quality, is often continuous and is accurately localized. Visceral pain on the other hand, has a distinctive dull quality which is difficult of description. It is often intermittent or spasmodic, and in sharp contrast to somatic pain it is imperfectly localized. Such descriptions can be most aptly applied to the headaches under discussion, of which there are two varieties. Those infrequent headaches in which a neuralgic element is prominent, and which were conceded to be possibly of dural origin, may be regarded as somatic pain. The common headache due to an intracranial tumour, to an epileptiform convulsion, or to an intracranial aneurysm, satisfies remarkably fully the criteria of visceral pain.

Visceral pain is the manifestation in consciousness of a protective mechanism. In the presence of any obstruction of its lumen, the intestine undergoes violent muscular contractions in order to rid itself of the obstruction. Although the intestine is insensitive to ordinary physical stimuli, it is now fully accepted that visceral pain arises only as a result of the adequate stimulus—an abnormal state of tension of the muscular walls. In the respiratory system, pain is almost entirely of somatic origin ; the visceral element has remained undeveloped, for the protective mechanism consists of a cough reflex. In certain diseases of the heart, the cardiovascular system is guarded against the dangerous strain of effort by a mechanism which produces anginal pain. Using this simile, the integrity of the central nervous system depends entirely upon an adequate supply of blood. In the presence of a tumour, this supply of blood is in danger. Headache may be regarded as visceral pain, indicating the perilous position of the brain, and a state of abnormal tension set up in the walls of its blood-vessels may be the adequate stimulus of visceral afferent fibres, the pathway of which is not yet clearly defined.

SUMMARY.

(1) This paper presents a study of the headaches provoked by intracranial tumours, with especial reference to the mechanism of their causation.

(2) The significance of the clinical varieties of these headaches is considered.

(3) Experiments are described which were performed in order to determine the sensitiveness or otherwise of the intracranial contents, and to elucidate the factors which provoke or relieve headache.

(4) The results of these studies are discussed in the light of the anatomy and physiology of the intracranial circulation, and of the physiology of the intracranial pressure.

(5) It is concluded that the dura mater is not the sensitive structure which is responsible for the characteristic headaches of intracranial tumour.

(6) It is suggested that the headache is caused by an abnormal state of tension in the walls of the cerebral blood-vessels.

It is a pleasure to offer my grateful acknowledgment to Professor Hugh Cairns, for suggesting the subject as worthy of research, for the facilities which are always available in his department to those interested in research, and for the stimulus of many fruitful discussions.

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"APHASIA" IN A PARTIAL DEAF-MUTE.

BY MACDONALD CRITCHLEY.

In an article contributed to the first volume of this Journal, Hughlings Jackson (1878) wrote: "No doubt, by disease of some part of the brain, the deaf-mute might lose his natural system of signs which are of some speech value to him." The case here recorded, sixty years later, furnishes strong support to Jackson's contention, although complete proof is still wanting.

Preoccupation with verbalization as the most obvious modality of language has diverted attention away from the non-verbal processes of speech. Obviously, spoken words are only one of several modes of "symbolic formulation and expression," and articulate speech is not essential in making known one's ideas or feelings. A tourist in a foreign country where the language is unfamiliar can contrive to make himself fairly well understood by calling upon the resources of gesticulation, just as he will manage to comprehend his entourage by studying their facial expressions and gestures.

At the outset it is necessary to be precise in our terminology. As Jackson taught, the word "pantomime," which should be restricted to that variety of dumbshow which aims at expressing an idea, should be distinguished from "gesture" which connotes those movements, especially of the hands and face, accompanying speech for the purpose of emphasis. Pantomime is silent acting while gesture is merely a kind of italicized speech. The relationship of pantomime to gesture is that of "propositionizing" to emotional utterance. It must be remembered that no sharp frontier divides gesture from pantomime—any more than emotional from propositional speech—and in some cases expressive movements can be assigned to either category.

The term "physiognomy" serves to denote the play of facial emotional movements, most of which are automatic rather than deliberate, and many of which are beyond the control of volition. This term also comprises the involuntary changes determined by emotional factors, mediated chiefly by way of the autonomic nervous system. Such phenomena as blushing, pallor, shivering, sweating, horripilation belong here.

Clearly, even articulate speech is at times nothing but gesture rendered audible. This view is borne out by the occurrence, in analogous form in

all languages, of certain onomatopœic words, where the meaning is adequately conveyed by the sounds themselves. Some philologists and phoneticists have gone much further in attempting to trace a far closer alliance between gesture and vocal speech. Paget, for example, regards speech as an elaboration of phonated buccal-labio-lingual gestures. He finds an intimate connection between the phonetics of a word and its meaning. The suggestion is that man originally expressed himself by gesture, and "as he gesticulated with his hands, his tongue, lips and jaw muscles followed suit in a ridiculous fashion, understudying the action of the hands. Later, movements of the jaws and mouth actually supplanted the manual gestures, when it was found the expiration of air through the oral cavities produced a wide range of audible mouth-gestures or voiced-speech."

Expressive Movements in Aphasic Patients.

In cases of aphasia due to focal cerebral lesions, the role of gesture and pantomime forms an interesting though neglected subject. It may be said in broad terms that articulate speech is usually affected far more severely than expressive movement. When the aphasic defect is slight the patient can usually communicate by signs in unmistakable manner, even though the right upper limb is powerless. The pantomime falls short of normal standards however in respect of precision and range; this defect is as a rule directly proportional to the degree of aphasia. In some instances of total speechlessness with dementia, almost all power of expressing ideas and even feelings is lost; to this inability to communicate by signs and by words, the term "asemasia" was proposed by Hamilton. Hughlings Jackson (loc. cit.) recognized three grades of disordered function: (1) defect of speech; (2) loss of speech, where the patient is practically inarticulate and where pantomime is impaired; and (3) loss of language, where pantomime as well as speech is completely lost.

Nevertheless, aphasic patients may occasionally betray exaggerated expressive movements of all types. This feature may be noted at times in patients with jargonaphasia. Recent conceptions, which follow Goldstein, van Woerkom and others in studying disturbances of the "total behaviour" in aphasic patients, confirm this. According to Goldstein (1936), patients with amnesic aphasia are persons acting in the world rather than thinking or speaking about the world, and in such, expressive movements may be excessive.

Deaf-mutes.

There is one set of circumstances in which gesture language entirely ousts verbalization from speech. In a deaf-mute articulate speech is

minimal, and an elaboration of pantomime becomes all-important. Here, a complex system of dactylology, with or without lip-reading, forms the usual channel for the interchange of ideas.

The question arises as to whether or not there exists an anatomical substratum comparable with the normal "zone of language" in the left hemisphere, and vulnerable to the usual morbid assaults. In other words, whether focal cerebral lesions can damage or destroy the execution of sign-language by a deaf-mute as Jackson originally hinted.

The following case-record demonstrates that a left-sided cerebral lesion can interfere with the performance of finger-spelling in a "partial" (i.e. acquired) deaf-mute:—

W. H. H., a man aged 42 years, first attended my out-patient clinic at the National Hospital, Queen Square, in 1930, on account of the effects of a stroke sustained six weeks before.

The patient was well until the age of 7 years when he gradually lost his hearing. As his disability steadily increased, he was taught finger-spelling. By the age of 14 years, being now stone-deaf, he was admitted to an institution for deaf-mutes. Here he remained three years; finger-speech was discouraged and he was taught lip-reading. After leaving the school he relied chiefly upon manual signs and finger-speech to communicate with others.

His stroke, which occurred on September 1, 1930, caused a right-sided paralysis, and for three days he was deprived of what little articulate speech had previously been possible to him. The paralysis improved considerably in the course of the next four weeks, and his speech also returned to some degree.

As soon as he was able to hold a pen, it was found that he could neither write nor perform on paper simple arithmetical calculations. It was also discovered that he could no longer lip-read. For the first few days after the stroke he was quite unable to understand people who communicated with him in finger-spelling. This ability returned in a few days, but he was still unable to reply upon his hands. His articulate speech was infrequent, and considerably altered; it was much too loud in tone, and he seemed "unable to regulate" his voice, so that when he wanted to emphasize a word, he merely raised his voice to a shout. The speech was furthermore dysarthric and ungrammatical; he seemed to rely very little indeed upon this means of communication.

He remained under observation for the next two years, during which time his condition changed little, if at all.

Repeated physical examination revealed a right-sided hemihypæsthesia, but no hemianopia; no loss of power in the arm or leg but a slight right-sided weakness of the face and tongue. The tendon-jerks were equal on the two sides and both plantar responses were flexor in type. No evidence of apraxia.

Investigations of the patient's aphasia were carried out through the intermediary of the late Rev. Mr. Bradbury, chaplain to the deaf and dumb institution, who acted as interpreter.

Some ability to lip-read was beginning to appear, but the defect was still very considerable. The power to understand others talking upon their hands had returned.

A large number of defects were present, however, in the patient's own efforts at finger-spelling. According to the interpreter the chief faults comprised:—

(1) Confusion of the vowels, viz. he might point to "A" instead of "E."

(2) His finger-speech no longer formed sentences but was short, "telegrammatic" and ungrammatical.

(3) If asked to indicate the five vowels he started correctly but was unable to finish. When asked to go through the alphabet he was at times unable to complete the task.

(4) The movements of the hands were manifestly erratic and jerky; "there is no smoothness about them." Possibly they were executed more slowly than usual, but the patient and the interpreter were not in agreement upon this point. According to the former . . . "my deaf friends say I go too quickly and that if I were to go more slowly I would get along better."

(5) Words were omitted, and wrong words were used.

Tests with writing, recognition of colours, clock-reading, word-building with cards, typing, and reading were executed pretty well on the whole. Calculations were carried out with some difficulty.

Here then is a partial deaf-mute who as the result of a left-sided cerebral lesion, presumably small and circumscribed in area, developed an "aphasia" as regards his dominant method of symbolic expression. Such a case recalls the idea at one time held by Liepmann that motor aphasia is a mere variant of motor apraxia ("apraxia of the lips and tongue") and this particular case might perhaps be regarded by some as an instance of "dactylological apraxia." The specialized use of the hands as organs of speech in the case of deaf-mutes, lends support to Liepmann's view.

The literature holds no record of any other such case. Closest in approximation is the description by Grasset (1896) of another deaf-mute who lost his ability to make hand-signs after a cerebral vascular lesion. The patient, an arteriopathic deaf-mute of 50 years, rather gradually developed signs of a cerebral softening. There was some lowering of the general intellectual level, so that he had ceased to be able to manage his business, and his memory and rate of comprehension had deteriorated. Nevertheless, he was able to read with understanding, and also to comprehend finger-talk in others. He was, however, unable to reply with the right-hand finger-alphabet but could do so promptly with the left hand. If asked to spell out the alphabet he started by indicating with difficulty the letter "A," then with more difficulty the "B," and then failed to sign the remaining letters. Using the left hand he could demonstrate the alphabet rapidly and correctly. If shown printed words and told to spell them on his fingers, he succeeded with his left hand but failed with his right. At the same time there was a difficulty in writing. The right arm showed

some defect of motor power and of co-ordination, though insufficient in degree to account for the failure to write or to finger-spell.

In this patient, however, the finger-spelling had always been carried out with the right hand only—as is the rule with deaf-mutes in France and the U.S.A. After the stroke, the patient was able to perform finger-spelling correctly with the left hand, though scarcely at all with the right. Such an inconsistency plainly reveals a different kind of speech affection than was present in my case, and is best recognized as an example of apraxia, or possibly of finger-agnosia (Gerstmann's syndrome). An integrity of all the preverbal processes which may loosely be described as "internal speech" seems to have been present in Grasset's case, but not in the case here recorded.

Grasset concluded that in the deaf-mute, a centre for manual speech develops in the cortex, independent of the motor area of the upper limb. He tentatively located this in the foot of the second frontal convolution of the left hemisphere.

In discussing the language of deaf-mutes it is necessary to draw attention to a very important though little known fact. Congenital deaf-mutes universally employ in addition to their complicated uni- or bimanual dactylology or finger-spelling, a kind of "natural sign-language." This is a sort of pantomimic shorthand, whereby a movement serves to indicate an entire word, a phrase, or even a sentence. The "natural" sign-language is not necessarily taught in schools (indeed its use may actually be discouraged). It is not committed to textbooks, and there are only a very few and rather inaccessible pamphlets on the subject. It is mainly "picked-up" by deaf-mutes in their institutions and passed on from one to another as a sort of tradition.

A number of interesting features are traceable in this sign language. In addition to its inherent advantages of rapid execution it possesses yet another outstanding merit. The natural sign-language is largely "international" and surmounts racial and linguistic barriers. Deaf-mutes of all nationalities have little difficulty in understanding and communicating with each other.

This universal comprehensibility follows because most of the gestures are obvious in their meaning, and represent a symbolism which is universally accepted and employed. These symbols belong to the category of "natural" signs, either because they mimic the specific appearance or function of the object concerned or because they are so traditional and ingrained as to be obvious to peoples of every race and age. In addition to these "natural" or "instinctive" gestures, there are a smaller number of "cryptogenetic" symbols where the meaning and origin are not self-

evident. Such gestures may vary from country to country, and even from one institution to another. Actually even these signs are not altogether empirical, but the various processes in their development have become distorted or eliminated, so that the end-result is no longer recognizable at sight.

There are still other circumstances where gesture language usurps—either habitually or on occasion—the place of articulate speech. In some primitive societies, gesture may constitute a *lingua franca* between peoples speaking divers languages which are unfamiliar. Such sign-languages exist amongst the Queensland aborigines (Howitt (1891), Roth (1897), Stirling; and among the North American Indians (Seton (1918), Tomkins (1926)). These have been adequately studied and documented. So similar are they to each other, and also to the natural sign-language of deaf-mutes, that they are mutually comprehensible. Many of the signs are identical and others so little different as to cause no doubt as to their meaning. These are striking observations which have been confirmed by various writers on many occasions.

It is not yet known whether a far-reaching likeness exists between these systems and the various other elaborate sign-languages which are practised. Although studies have been made of the gestures employed in the Hung Secret Societies of China (Ward); the Neapolitan slums (de Jorio): the Trappist and other monastic orders (Herrgot; Aungier), no work of a comparative character has been attempted. A superficial study suggests that there is but little similarity between these systems and the "natural" sign-languages of the deaf-mutes and the aborigines. The factors of ritual and of secrecy no doubt go far to obscure the meaning of the other sign-languages and introduce an element of artificiality.

In the case of the deaf-mute patient described in this paper, the "natural" sign-language was not impaired. The circumstances were unusual, however, in that he had never been proficient in this means of communication and preferred lip-reading or finger-spelling. This may be ascribed to a variety of reasons, and especially to the fact that hearing was intact for the first few years of life, during which period articulate speech developed normally. For this reason the patient cannot be regarded as an example of "complete" or congenital deaf-mutism. Hughlings Jackson's surmise therefore remains unverified inasmuch as it explicitly referred to a natural system of signs and not to finger-spelling. It is justifiable to suggest that a much more severe lesion would be required to abolish the more primitive sign-language than the elaborate system of dactylology.

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GLIOMATOSIS CEREBRI.[1]

BY SAMUEL NEVIN.

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INTRODUCTION.

FROM time to time occasional reports of cases, characterized pathologically by a diffuse cellular overgrowth throughout the wide areas of the cerebral hemispheres, have appeared in the literature. These have generally been regarded as diffuse tumours, but they have varied considerably as regards the actual type of the cell constituting the overgrowth and they have been described by the different authors under different titles.

In 1910 Landau, under the title "Diffuse Glioma of the Brain," described the case of a male, aged 29, who died suddenly after a three years' history of intermittent headaches and epileptic attacks. The patient showed no physical signs apart from an intention tremor of the left arm and leg, and a slight ptosis of the left eye. At autopsy there was found a diffuse enlargement of the anterior part of the right cerebral hemisphere, which showed on section softening and œdema of the white matter, with slight loss of colour and some increase in thickness of the grey matter. Microscopical examination revealed a widespread but very variable gliomatous degeneration of the cortex and the thalamus on the left side. The cells which were regarded by the author as undifferentiated glial cells, were superimposed upon the normal tissues, with accumulations round the nerve cells and along the vessels. There was calcification of the blood-vessels and in the nerve cells. The author considered the condition as a

[1] From the Hospital for Nervous Diseases, Maida Vale.

diffuse glioma which had arisen at different points in a congenitally abnormal tissue, and had spread by continual involvement of other regions in the pathological process. Hildebrandt (1906), under the title of "Gliomatous Hypertrophy" of the right cerebral hemisphere, and Schwartz and Klauer (1927), under the title of "Diffuse systematic overgrowth of the glial apparatus of the brain," have recorded somewhat similar cases.

Cassirer and Lewy (1923) described the case of a woman aged 37, who, after a nine months' history of failure of vision and epileptic attacks, died following an operation for relief of increased intracranial pressure. At autopsy the right hemisphere was found to be swollen, and of slightly increased consistency. Sections showed large areas of demyelinization in the right cerebral hemisphere, which had arisen as the result of a mature glioma. This in its centre had produced mostly fibres, but in its periphery it was very cellular and grew in a fingerlike manner into the cortex and even through this into the pia. The author regarded the case as exemplifying a blastomatous type of diffuse sclerosis.

More recently Foerster (1934) has described, under the title "Central Diffuse Schwannosis" in Von Recklinghausen's disease, the case of a girl, aged 11, who within a period of six weeks developed severe headaches, loss of vision, and weakness of the left side. The patient had skin changes as in Von Recklinghausen's disease, namely numerous pigmented spots and small isolated fibromata on the trunk and limbs. Death occurred with symptoms of increased intracranial pressure. At autopsy there was found a great enlargement of the basal ganglia and thalamus on both sides. There was also diffuse swelling of the brain stem. Microscopical examination showed a dense cellular overgrowth in these regions composed of elongated, cigarette-like nuclei, which were arranged parallel to one another along the nerve fibre bundles. These cells were also found over wide areas of the cortex, but less densely placed except underneath the pia and along the blood-vessels. Santha (1935-36) has described a similar case under a similar title, which, however, showed no skin changes or other evidence of Von Recklinghausen's disease.

It is proposed in the following paper to describe three cases with similar pathological features, and to discuss the questions raised in reference to this group of cases.

Case 1.—Clinical history: E.R.P., a married woman, aged 23, was admitted to the Hospital for Nervous Diseases, Maida Vale, March 25, 1936, under Dr. Blake Pritchard.

The family history was negative. She had been married a year and had no child. She was in her usual health until ten months before admission to hospital,

when she began to suffer from headaches, failing memory, and attacks of loss of consciousness. All these symptoms appeared at about the same time, and led to an immediate cessation of her work as a waitress. The attacks were uniform in character; she stopped what she was doing, stared vacantly in front of her, and except for slight flickering of the fingers was motionless. The attacks varied in frequency from as many as seven a day to a day of freedom. Headache followed the attacks, but soon began to come at other times and more frequently as the illness progressed. She was easily excited, complained of her poor memory for recent events, but continued her housework up to the date of admission to hospital.

On examination she was found to be mentally dull, apathetic and slow in movements, of notably defective memory, especially for recent events, but able to

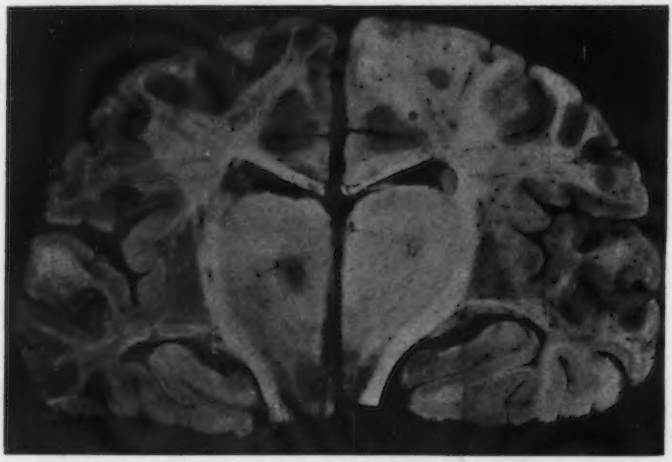


FIG. 1. *Case 1.*—Vertical section through the brain (anterior view) showing the enlargement and pallor of the thalami, the enlargement of the hippocampus, and the pallor and widening of the cerebral cortex in circumscribed areas.

co-operate moderately well in her examination. She showed no disorientation. The speech function was normal. There was bilateral papillœdema of about 4-5D. In other respects physical examination was wholly negative; the reflexes, sensation, and the motor system all being normal. The cerebrospinal fluid was under a pressure of over 300 mm., but was normal in all respects. The Wassermann was negative in the blood and cerebrospinal fluid. The lumber puncture led to symptoms of a cerebellar pressure cone. Ventriculography by Mr. McKissock showed general narrowing of the bodies of both ventricles, but the patient died before a right temporal decompression could be performed.

Post-mortem examination.—The brain only was available for examination. It weighed 1,340 grm., and of this the cerebral hemispheres weighed 1,190 grm. A large cerebellar pressure cone was present, and the convolutions were slightly flattened. The cortex of the under surface of frontal and anterior temporal lobes was granular and irregular, and from it the arachnoid and blood-vessels stripped

less easily than normal. In places the granulations were so coarse that they overlapped branches of the middle cerebral artery, and generally the blood-vessels indented the cortical surface, leaving their pattern imprinted thereon when removed. This abnormal granularity extended into the island of Reil and along the margins of the posterior ramus of the Sylvian fissure and also along the cingulate gyrus. It was symmetrical in its distribution in the two hemispheres.

The brain was sectioned vertically, revealing a diffuse pathological change throughout the greater part of the cerebral hemispheres (fig. 1). The thalami were generally enlarged, pale, and firmer than normal, causing narrowing of the lateral ventricles, and flattening of the hippocampus and hippocampal gyri. The massa intermedia was also enlarged and firm. In the cerebral cortex there was pallor and enlargement of the grey matter, with consequent loss of contrast between it and the white matter, and the distribution of these changes corresponded closely with that of the surface granulation already described. They were, however, most severe in the anterior parts of the temporal lobes, where the cerebral tissue as a whole was softer than normal, and the fissures increased in depth. The caudate and lenticular nuclei appeared normal to the naked eye except that the under part of the left caudate nucleus in its anterior part was paler, larger and softer than normal. The upper part of the mid-brain was also similarly involved, but the pons medulla and cerebellum and the walls of the ventricles showed no abnormality to the naked eye.

Microscopical examination revealed a diffuse and very symmetrical cellular overgrowth throughout wide areas of the cerebral hemispheres. This was associated with a varying new formation of glial fibres and secondary changes in the essential nervous elements, which were, however, slight in comparison to the degree of the new cell formation. The detailed changes will now be described, first in the thalamus, then in the anterior region of the temporal lobes, after which their distribution throughout the cerebral hemispheres and brain stem will be followed.

Thalamus.—In the thalamus the new growth was formed by cells with round, oval, and also elongated nuclei whose size and granular chromatin structure in general resembled that of neuroglial nuclei. There was considerable variation in the density of the chromatin network ; the nuclear membrane was well defined, and no cell body was seen with ordinary nuclear staining. There were all variations in shape between completely round and pure rod-like nuclear forms, but oval and smoothly elongated forms predominated, and alterations in the thickness of the latter along their length produced bizarre nuclear shapes. The cellular overgrowth was fairly evenly and diffusely spread throughout the thalamus, but it was condensed around the medium-sized blood-vessels where strands of elongated nuclei were found running parallel to their long axis. There was also irregular clumping of nuclei round the nerve cells.

A great overgrowth of neuroglial fibres accompanied the new cell formation. This formed a dense network throughout the whole thalamus, with striking condensations along the blood-vessels, either parallel or more irregularly arranged. There was enlargement of the perivascular spaces, and in places the adventitia of the vessels was adherent to the surrounding gliosis, while glia-like cells were found infiltrating the outer vessel coats. Hæmorrhages into the outer layers of the vessel sheaths, between the vessel and the surrounding brain tissue, and sometimes within the latter, were frequently observed.

It was found very difficult to stain the cells of the new growth by impregnation

methods. Globus' modification of Cajal's gold chloride method, the fourth variant of Achúcarro's tannin silver method, and Davenport's silver stain were used unsuccessfully, but Hortega's silver carbonate method for astrocytes revealed that they consisted of unipolar and bipolar spongioblasts and astrocytes. Unipolar spongioblasts with rounded, small cell body, and short indefinite process were not numerous. The bipolar spongioblasts formed a larger part of the growth, as the elongated nuclei belonged for the most part to cells of this type. The protoplasm stained a light brown, was small in amount, and tailed off at both ends of the cell into a long fibre process, the exact limits of which could not be traced in any one field. The astrocytes varied very much in size, shape, and form. In some cells, especially those with irregular shaped nuclei, there was very little cell protoplasm, and the cell processes were short, whereas in those with oval or rounded nuclei the cells more closely resembled mature astrocytes. The irregular shaped astrocytes appeared to be transition stages between the spongioblasts and the more mature astrocytes. In all cells the nuclei were darkly granular and heavily impregnated (fig. 2*a*).

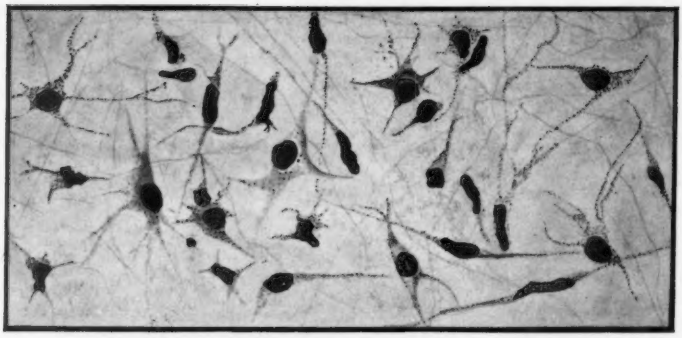
This cellular and neuroglial overgrowth did not produce severe alteration in the essential nervous elements of the thalamus. There was no gross reduction in the number of the nerve cells but they appeared more widely separated than normal and contained a few large droplets of fat which stained reddish yellow with Scharlach R. In myelin preparations the internal capsule was darkly stained and the thalamus was only slightly paler than normal, and these also showed that the cellular overgrowth round the blood-vessels gave rise to the displacement of the myelinated fibres adjacent to the vessels as is illustrated in fig. 3.

Anterior temporal lobe.—In this region the changes were typical of those affecting wide areas of the cerebral cortex. The density of the cellular overgrowth was greatest underneath the pia (fig. 4), where bundles of elongated or oval nuclei lying in a fibrillar matrix were placed either in a horizontal, vertical or oblique direction. The arrangement was not always regular, and masses of cells intermingled with the strand-like bundles produced a very varied appearance. The overgrowth extended upwards underneath the pia, forming nodular or wart-like elevations, completely irregular in shape and form, on the cortical surface. In many places it had broken through this membrane, and become adherent to the outer wall of the vessels. These were the microscopical appearances corresponding to the granularity of the cortex observable by the naked eye. Hæmorrhages had occurred into the thickened leptomeninges and between the pia and the cortex. In the deeper parts of the molecular layer and throughout the cellular layers of the cortex the overgrowth was diffuse and irregular. In some places, however, the nuclei were clumped round the nerve cells, and cellular strands were prolonged from the subpial zone along the blood-vessels right through the cortex, and even into the medulla (fig. 5). In the subcortical zone the nuclei were round and perhaps smaller than those in the cortical layers, while the cellular increase gradually disappeared in the depths of the white matter. Numerous small hæmorrhagic foci were present in both the grey and white matter, and irregular cavities also occurred in these structures. Two factors seemed to play a part in their production, enlargement of the perivascular spaces, and the absorption of the hæmorrhages.

The new growth underneath the pia was composed mostly of strands of bipolar cells associated with dense piloid masses of fine glial fibres, but in some parts the gliosis was a dense network, and numerous astrocytic cells were present. The latter predominated in the deeper parts of the molecular layer. In the cortical cell layers

PLATE V.

(*a*)



(*b*)

(*c*)

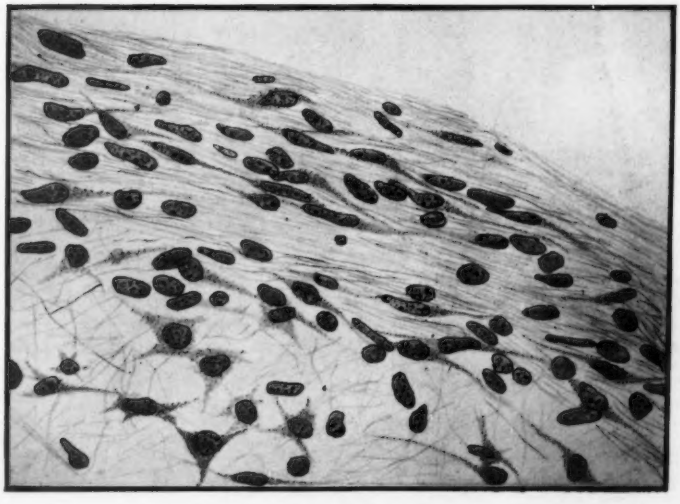


FIG. 2.

To illustrate paper by Samuel Nevin.

PLATE VI.

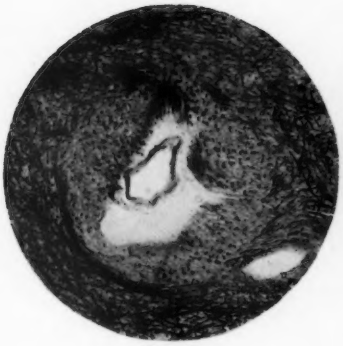


FIG. 3.

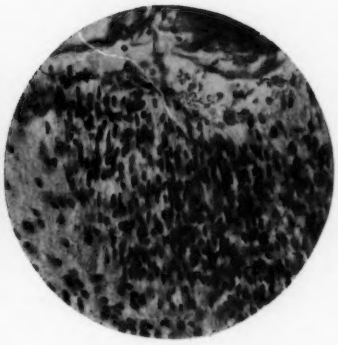


FIG. 4.

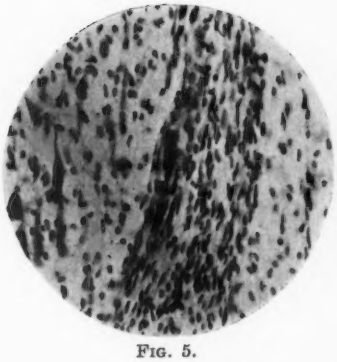


FIG. 5.

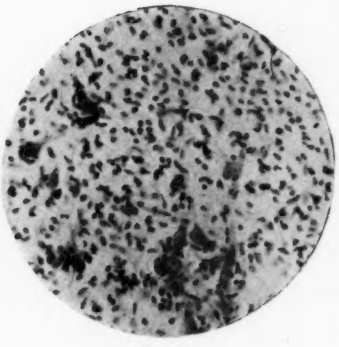


FIG. 6.

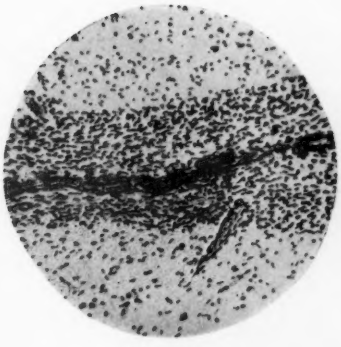


FIG. 7.

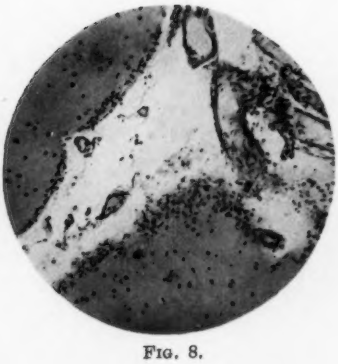


FIG. 8.

To illustrate paper by Samuel Nevin.

the glial overgrowth was a very loose open network formed of large thick fibres which stained better with iron hæmatoxylin than with victoria blue, and unipolar, bipolar, and astrocytic types of cells were scattered fairly evenly throughout the cortex (fig. 2 *b* and *c*). Bipolar forms predominated in the cellular strands along the blood-vessels. In the subcortical white matter the gliosis was a fine dense network staining darkly with victoria blue, and the cells were mainly astrocytic with some variation in size and shape. This variation in the fibre production in the grey and white matter seemed to reflect the normal difference in the neuroglia in these structures. It is also interesting to note that Nissl preparations showed faint staining of the cell processes of the bipolar spongioblasts.

This new growth resulted in considerable loss of nerve cells, especially the granular cells. There was alteration and distortion in the arrangement of those remaining, so that the cortical layers were not recognizable in the areas of greatest growth (fig. 6). The residual nerve cells were lying at all angles to the surface of the cortex, some even being actually reversed in position, and the dendrites also shared in the distortion, being curved in unusual manners. Such cells were more

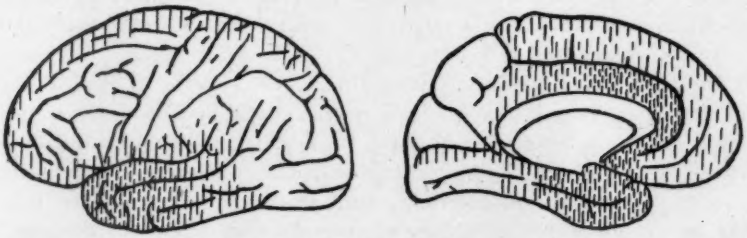


FIG. 9. *Case 1.*—Diagram showing the distribution of the cellular overgrowth in the cortex.

fusiform than normal, and they contained small accumulations of fat, staining reddish yellow with Scharlach R at the base of the cell or extending round the nucleus. There was also degeneration of the myelinated fibres in the cortex and subcortical white matter, but the tangential fibres even in the most affected areas were still to be seen, although widely separated amidst the cellular overgrowth.

General Distribution of the Microscopical Changes.—The severe cortical changes, leading to gross distortion of the nerve cell layers, were confined to a small area of the anterior and medial aspect of the temporal lobes. The more widespread changes, the distribution of which is illustrated in fig. 9, were less severe. Although there was still considerable loss of nerve cells the cortical layers were still recognizable, and the diffuse overgrowth in the deeper parts of the cortex was in striking contrast to the dense subpial infiltration (fig. 7). The changes gradually diminished towards the normal cortex, where the subpial overgrowth became reduced to a layer a few cells thick and there was only a slight excess of irregular and elongated neuroglial cells in the deeper layers.

The new growth spread from the affected cortical areas through the basal ganglia, and was continuous with that in the thalamus. It was, however, much less in the basal ganglia, and the gliosis was greater in the fibre bundles and internal capsule than in the grey matter. The optic chiasma was intensely gliosed and here dense

piloid masses of fibres were found running along the septa between the nerve bundles and spreading as an open network irregularly throughout the whole structure, The margin of the mid-brain was encircled by a slight subpial overgrowth, while the dorsal part of this structure contained a diffuse cellular and glial proliferation. This dorsal infiltration extended down the pons and medulla to the upper part of the spinal cord where slight changes were found in the grey matter, especially in the posterior intramedullary root zone. The general structure of the cerebellum was normal, but occasional foci of subpial overgrowth similar to that seen in the cerebral cortex were found on the anterior and inferior surface (fig. 8). The fourth nerve was sectioned at the side of the mid-brain, and showed definite involvement of the nerve by bundles of new cell formation, intensely fibrillar, and staining with neuroglial stains similar to the subpial overgrowth. This seemed to have grown from the brain stem out into the nerve. A similar appearance was observed at the junction of the upper posterior cervical roots with the spinal cord.

Summary of Case 1.

The case was characterized clinically by symptoms of gradually increasing intracranial pressure associated with general mental dullness, marked failure of memory, and epileptic attacks.

The pathological process consisted in a new growth of spongioblasts and astrocytes, irregular and variable in size, shape, and form, throughout wide areas of the cerebral cortex, the basal ganglia, thalamus and upper part of the brain stem. This new growth was implanted on the normal structure of the nervous system, and produced comparatively slight secondary changes in the essential nervous elements. The distribution of the cellular overgrowth was not completely irregular, but bore a definite relationship to the normal structure of the nervous system. In the cortex it was greatest underneath the pia mater, where the predominant type of cell was a bipolar spongioblast with dense fibre formation. In the cellular layers of the cortex the overgrowth was more diffuse and less densely arranged. The cells were spongioblasts and astrocytes in irregular arrangement, and the fibre formation was a coarse, wide open network difficult to stain. The subcortical zone of the white matter was more affected than the deeper parts of the white matter, and here the growth was mainly astrocytic, with a dense fine glial network. In the thalamus a spongioblastic and astrocytic growth with dense fibre formation was present.

Case 2.—Clinical History: H. S., an unmarried woman, aged 54, was admitted to the Hospital for Nervous Diseases, Maida Vale, September 12, 1936, under Dr. Russell Brain.

The family history was negative. The patient had been subject to epilepsy all her life. The attacks were infrequent and mostly minor in character, but from time to time major attacks occurred. She was in her usual health up to four years before admission to hospital, when it was observed that she was losing her initiative and her interest in life generally. A year later these symptoms were more

obvious, and she had become completely self-centred and emotionally unstable. The advance of the illness continued to be slow up to six months before her death, when a rapid change for the worse took place. The patient's mental state deteriorated rapidly. She became completely apathetic, with no inclination to do anything but feed herself, and she also became incontinent of urine and fæces, and at times hid her excreta under the cushions and the piano. Failure of memory, according to the relations, was not an outstanding feature, although it was undoubtedly present with the gross mental deterioration. About this time progressive weakness of the right arm and leg was first noticed. She was admitted to hospital in a very drowsy and stuporose state, from which she could just be roused. Early papillœdema was present in both eyes, greater on the right side. There were extensive areas of pigmentation on the neck and upper limbs, similar to the

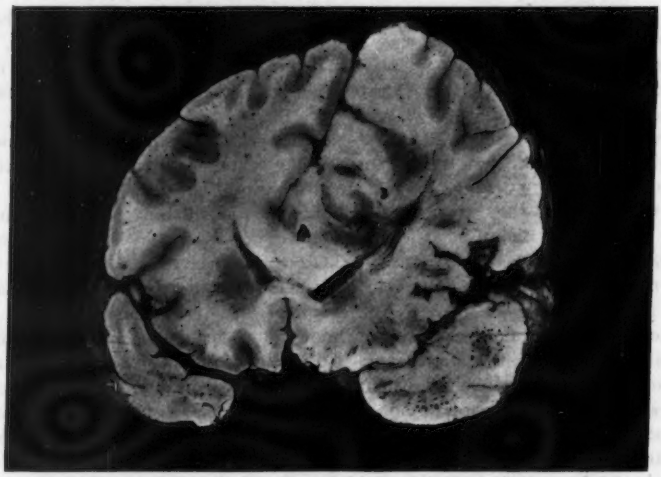


FIG. 10. *Case 2.*—Vertical section through the brain showing the enlargement of the left hemisphere, the severe changes round the left cingulate sulcus, the loss of contrast between the grey and white matter, and the honeycombing of the white matter.

cutaneous pigmentation of Von Recklinghausen's disease. There was complete right-sided flaccid hemiplegia. The cerebrospinal fluid was not examined, and X-rays of the skull were not taken. She gradually became unconscious, and died twenty-four hours after admission to hospital.

Post-mortem examination.—The brain only was available for examination. A small firm greyish-white tumour, about the size of a hazel nut, was present in the suprapituitary region posterior to the stalk of the pituitary. The brain weighed 1,093 grm., and of this the cerebral hemispheres weighed 957 grm. The left cerebral hemisphere forwards from the fissure of Rolando was larger than the right. There was a moderate cerebellar pressure cone, and a herniation of the uncus on both sides, that on the left side being larger, and also somewhat rough and nodular. The cortex on the under surface of the frontal lobes, especially on the

left side, was somewhat granular in appearance, and less smooth than normal. There was a slight purple discoloration of the margins of the posterior ramus of the left Sylvian fissure for a distance of about one and a half inches from its commencement. Similar areas of discoloration, only darker, were found on the left middle frontal convolution about its centre, and on the anterior part of the medial aspect of the superior frontal convolution.

The brain was sectioned vertically, and this revealed a diffuse pathological change throughout wide areas of the anterior parts of the hemispheres (fig. 10), consisting in increased depth of the cerebral cortex, loss of normal contrast between the grey and white matter, and a honeycombed appearance of the subcortical white matter. The anterior part of the left cingulate sulcus was greatly increased in depth, and the surrounding grey matter was two to three times its normal width. It was also paler and softer than normal, and had a somewhat translucent appearance. In the grey matter at the foot of the sulcus, and about the level of the genu of the corpus callosum there was a small area of darker discoloration, which felt gritty to the touch owing to foci of calcification. The subjacent white manner was somewhat dark, and in one or two places irregular fissures had appeared in the tissue.

Similar, only less severe, changes were present over the whole inferior and medial surface of the left frontal lobe. They extended backwards involving the anterior part of the temporal lobe, the island of Reil, and the margins of the posterior ramus of the Sylvian fissure, which were adherent to one another. In these areas the underlying white matter had a honeycombed appearance, especially in the subcortical zone. Where this appearance of the white matter was most marked the pallor of the grey matter was greatest, and in such areas the line of demarcation between these structures was not visible. In the right hemisphere the changes were much less extensive and confined to a small area round the anterior part of the cingulate sulcus, and in the anterior part of the temporal lobe. The basal ganglia were normal in appearance apart from slight pallor of the antero-lateral parts of the left lenticular and caudate nuclei. The anterior part of the corpus callosum was broader than normal, causing some outward and downward displacement of the anterior horns of the ventricles. No changes to the naked eye were visible in the thalamus or posterior part of the hemispheres, nor in the cerebellum or brain stem.

Microscopical Examination revealed that the naked eye pathological changes were produced by a diffuse cellular overgrowth throughout wide areas of the cerebral hemispheres. This will be described in detail in sections taken from the medial aspect of the left frontal lobe, and the distribution of the changes throughout the hemispheres will then be followed.

Left Frontal Lobe.—In the grey matter surrounding the anterior aspect of the cingulate sulcus a dense cellular overgrowth, composed of cells with round, oval and irregular-shaped nuclei, extended from the surface to the subcortical white matter and obliterated practically entirely all traces of the normal cortical structure. The nuclei were darkly granular, varied much in size and shape, and no cell body was seen with ordinary stains. Underneath some parts of the cortex fibrillar bundles of elongated nuclei were seen running parallel to the surface and intermingling with fibrous tissue growth from the leptomeninges, while in other parts dense masses of rounder nuclei projected from the surface in small nodes. Here and there foci of diffuse hæmorrhage were present and the blood-vessels were adherent to the cortex

and their outer walls infiltrated with cells from the surface overgrowth. The moleculer zone was filled with masses of more or less rounded nuclei, but in the cellular layers the new-formed cells were more evenly arranged throughout the tissue. Occasionally they occurred in clumps of three or four, or in short chains. Amitotic division could be seen with the formation of two very unequal nuclei. They practically filled the whole field, but isolated nerve cells were found throughout the whole depth of the cortex (fig. 12). The capillaries were very congested, and irregular masses of calcification were found in relation to the small blood-vessels, the walls of which showed fibrous thickening and endothelial proliferation. In the subcortical white matter the nuclei were smaller and rounder and very evenly arranged.

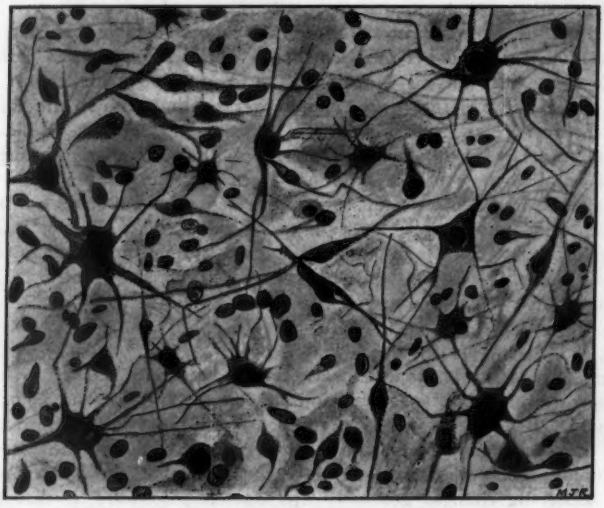


FIG. 11. *Case 2.*—Camera lucida drawing from a preparation of the grey matter beneath the left cingulate sulcus stained by Hortega's silver carbonate method for astrocytes. The varied size and shape of the astrocytic and spongioblastic cells are illustrated.

Impregnation by Hortega's silver carbonate method for astrocytes revealed the neuroglial origin of the new growth and all varieties of cells from immature spongioblasts to fully developed astrocytes were found. In the cellular layers of the cortex there were numerous large astrocytes of varying shape and form with large protoplasmic body and long coarse processes, and also large bipolar cells with terminal processes. These cells formed, however, only a small part of the overgrowth, because in the meshes of the fibrillar network formed by their processes lay numerous small unipolar and bipolar spongioblastic cells. Some of these showed a very sharply outlined cell body with fine terminal processes, but the majority showed a lightly stained body, with a coarse and faint cell process which could not be traced very far from the parent cell body. Many of the nuclei, however, showed no recognizable

cell body, most likely owing to the immaturity of the cells (fig. 11). The appearance was not, however, uniform throughout the whole depth of the cortex. In the subpial zone there were more numerous mature spongioblasts and astrocytes of medium size with long thick processes extending into the deeper parts of the molecular layer, while in the white matter small astrocytes predominated. The victoria blue stain for neuroglial fibres reflected the difference in cellular forms in the different cortical layers. A dense marginal gliosis of varying thickness filled the outer part of the molecular layer from which long thick processes extended inwards. In the cortex itself there was only an open network of thick pale fibres except along the small blood-vessels where parallel bundles of fine dark fibres were present (fig. 13). In the subcortical white matter, however, the gliosis was a dense fine network, with special condensations round the blood-vessels, so that there was a striking contrast between the glial formation in the grey and white matter (fig. 14).

The cellular overgrowth just described led to considerable but not complete destruction of the essential nervous elements. Myelin stains showed pallor of the subcortical zone, but isolated fibres with varicosities on their course occurred regularly in the midst of the dense cellular overgrowth. Also in the cortex fragments of the vertical and horizontal fibres were still to be seen. Residual nerve cells, mostly the large pyramidal cells, were also found regularly throughout the cortical layers. In most of these no Nissl granules were seen, but a greenish granular appearance of the protoplasm was present, due to lipoid accumulations in the cells at one or other pole, or right round the nucleus. This stained reddish with Scarlach R. Some of the pyramidal cells had become rounded or fusiform, and elongated in a direction vertical to the cortical surface, while in some the dendrites were twisted and curved in unusual manners.

The Microscopical Distribution of the Cellular Overgrowth.

This was much greater than the area of macroscopical change. On the left side the new growth was most severe round a line drawn from the cingulate gyrus to the island of Reil, and except for the region round the Sylvian fissure the medial areas of the hemisphere were more severely involved than the lateral. The entire frontal lobe was more or less involved, but in the parietal and temporal lobes the changes gradually disappeared posteriorly so that they were restricted at the termination of the Sylvian fissure to a small area of the upper margin of the fissure. In the anterior and medial aspects of the left temporal lobe the new growth was widespread and intense. In the right hemisphere it was much less extensive and more closely confined to the area of macroscopic change. There were no definite changes in the thalami, but the upper part of the brain-stem was involved round the central canal.

In following the distribution of the new growth, all degrees of pathological change were found, from an area of the cortex where only a few remaining nerve cells and fibres were present in the midst of a dense new cell formation, to an area where the structure of the cortex appeared normal and only a few pathological cells were scattered around and between the nerve cells. A characteristic feature in the less affected areas was the clumping of small-sized astrocytes and spongioblasts around the nerve cells (fig. 15).

Even in the less affected areas the subjacent white matter generally showed intense gliosis, and this was especially marked on the medial surface of the right frontal lobe, where there was not, however, a corresponding degree of demyelinization. In the left

PLATE VII.

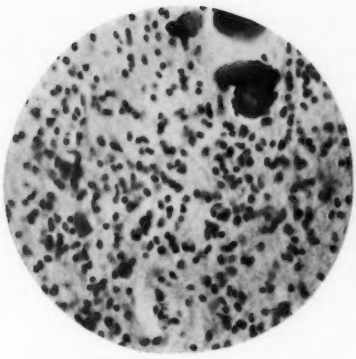


FIG. 12.

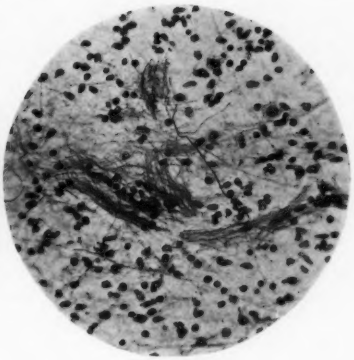


FIG. 13.

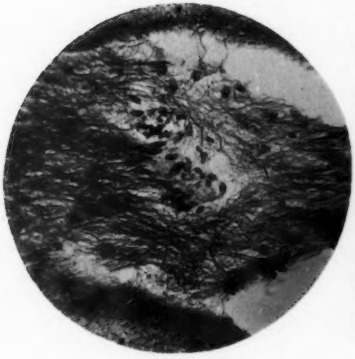


FIG. 14.

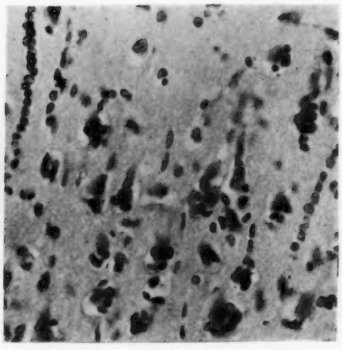


FIG. 15.

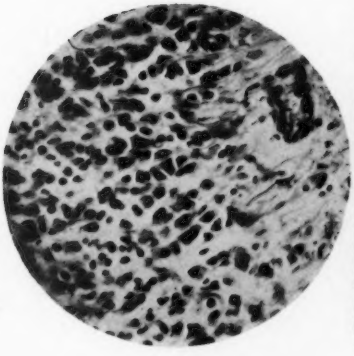


FIG. 16.

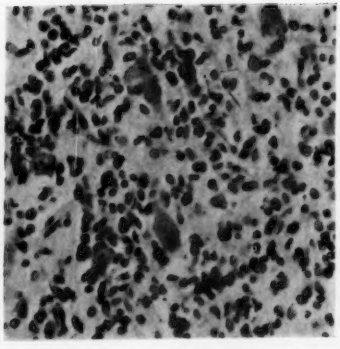


FIG. 17.

To illustrate paper by Samuel Nevin.

hemisphere the gliosis in the white matter had spread widely throughout the anterior two-thirds of the hemisphere, producing demyelinization, and oval and elongated fissures occurred in the sclerosed tissue. This cavitation was the cause of the honeycombed appearance in the brain observable with the naked eye. These cavities sometimes contained vascular channels consisting only of an endothelial lining and a fibrous tissue coat which varied very much in thickness, and was in some places adherent to the glial margin of the cavity. In the anterior part of the left temporal lobe the gliosis in the white matter was very intense, so that in some places it spread outwards into the cellular layers of the cortex as a dense network. The adherence of the cortical margins of the Sylvian fissure was produced by densely fibrillar and cellular bundles passing in all directions round the Sylvian vessels, uniting these to each other and to the cortex. Below the fissure, despite the continuity of tissue, the overgrowth was slight in comparison with that in the superior margin.

The dense gliosis of the white matter of the left frontal lobe stopped abruptly at the margin of the caudate and lenticular nuclei. In these structures which showed a moderate cellular overgrowth the gliosis was a loose open network, with fibrillar accumulations along the small blood-vessels exactly similar to the condition already described in the cortex of the anterior part of the cingulate gyrus. Also, in the anterior part of the internal capsule, the anterior commissure, the optic chiasma and the fornix, the fibrillar nature of the new growth was in striking contrast to that found in the adjacent cellular areas of the nervous system. There was no demyelinization in these structures.

The walls of the anterior parts of the lateral ventricles were intact, but they were surrounded by a thick gliosis, which was irregularly cellular, and contained large accumulations of ependymal cells and numerous corpora amylacea.

The overgrowth in the brain stem spread outwards from the central canal and affected the dorsal part of the mid-brain. It was intensely fibrillar and piloid masses of glial fibres projected into the lumen of the canal. There was also marginal gliosis round the medulla and upper part of the spinal cord. In these latter areas the neuroglial nuclei showed greater variation in size and shape than normal, but there was no definite increase.

In the posterior parts of the cerebral hemispheres, clearly uninvolved in the general overgrowth, foci of marginal gliosis were found in different places associated with groups of neuroglial cells in the subjacent molecular layer. The neuroglia in the cellular layers did not appear increased, but the variation in shape and form of the astrocytes appeared greater than normal, while in the white matter perivascular foci of neuroglial cells were sometimes found.

Focus of Anaplastic Tumour Formation in the left frontal lobe.

In the white matter underneath the superior frontal sulcus, anterior to the genu of the corpus callosum, an oval area of complete demyelinization three millimetres wide and six millimetres broad was found. The anteroposterior length of the area was not determined, but it was not much more extensive than the breadth. This was caused by a new growth of elongated, bipolar or pyramidal cells with round or oval nuclei arranged irregularly or in a radiating manner round the blood-vessels. Lightly-stained cell processes connected with the thin fibrous tissue sheath of the vessel walls, but not other cell processes or neuroglial fibres were stained (fig. 16). This focus of cellular overgrowth, which could be classified as a spongioblastoma multiforme, was quite distinct from the more widespread changes because it had

completely replaced the normal nervous structure and formed its own blood supply, and was clearly spreading as a single tumour from its point of origin. The cells in the tumour bore little, if any, resemblance to neuroglial cells, mature or undeveloped, and were stained to some extent by iron hæmatoxylin and van Gieson, and Davenport's silver stain, while the cells forming the general overgrowth were unstained by these methods, and their derivation from neuroglial cells was clear.

Developmental abnormalities and general changes in the nerve cells.

In the white matter underneath the calcarine fissure there was a slit-like cavity lined by ependymal cells surrounded by a mass of dense gliosis. Also in the upper part of the spinal cord the anterior fissure was absent over the first cervical segment, so that nerve cells were found underneath the anterior surface, and the anterior columns were spread over the lateral surface of the cord. At this level there was also cavitation along the posterior septum.

The nerve cells in the thalamus, brain stem and uninvolved areas of the cortex very frequently showed fatty accumulations in one part or other of the cell body. The significance of this pathological change was not clear. It was also very difficult to decide if slight alterations in the size and form of the larger pyramidal nerve cells in uninvolved cortical areas were greater than normal, but detailed studies of the architectonics of the cerebral cortex were not made.

The Suprapituitary Tumour.

Microscopically this tumour had the structure of a neurofibroma in which there was also present numerous thick-walled blood-vessels of varying size. In parts of the tumour these abnormal vessels were so numerous, and filled so much of the field, that they could very well be regarded as a composite part of the tumour, which might therefore be more adequately described as an angioneurofibroma.

Summary of Case 2.

The case was characterized clinically by a life history of epilepsy, four years' history of mental deterioration, failure of memory and character changes. Pigmentary skin changes as in Von Recklinghausen's disease were present. Death followed the development of symptoms of increased intracranial pressure and gross right-sided hemiplegia. The pathological process consisted in a new growth of spongioblasts and astrocytes, irregular and variable in size, shape and form, throughout wide areas of the anterior parts of the cerebral hemispheres, especially on the left side and involving also the brain stem. This new cell formation was superimposed upon the essential nervous elements, producing in these structures severe secondary changes in the areas of greatest growth. It was accompanied by a varying gliosis, which was not completely irregular, but bore a definite relationship to the normal structure of the nervous system. In the white matter this was a fine dense network, arising from small astrocytic cells, whereas in the grey matter the glial increase was a coarse open network, formed for the most part by the processes of large astrocytic and spongioblastic cells, except

along the small blood-vessels, where bundles of fine fibres were also present. An anaplastic focus of true tumour formation was found in the midst of the general cellular overgrowth, and a neurofibroma was also present in the suprapituitary region.

For the following case I am indebted to Dr. Gordon Holmes. The notes are from the routine clinical and pathological records of the National Hospital.

Case 3.—Clinical history: L. T., a man aged 27, was admitted to the National Hospital, May 7, 1909, under Dr. Gordon Holmes.

The family history was negative. As a youth he was subject to fainting attacks, the exact nature of which was not clear. At the age of 14 he suffered a blow on the head, and was unconscious for two hours. Otherwise he was well up to two and a half years before admission to hospital.

At this time he began to complain of epileptic attacks, headaches and loss of memory. The epileptic attacks, which were infrequent but generally severe, were preceded by a cramping, tingling pain in the right side of the face just before consciousness was lost, and followed by a transitory weakness of the right side. The headaches were very variable, and often localized behind the eyes. The symptoms gradually progressed up to admission to hospital. Examination revealed a marked failure of memory for both recent and remote events, and also some difficulty in remembering the names of objects. There was no mental or speech disturbance. Papillœdema developed under observation and apart from this the only abnormal physical signs were a slight lower right facial weakness, and a slight loss of sense of position in the right arm and leg.

In a two-stage operation Sir Victor Horsley performed a left cerebral decompression on the clinical diagnosis of a left parieto-temporal tumour. No definite tumour formation was located, and he was discharged fairly well and able to walk about, on July 5, 1909. This improvement was only maintained for a short time, and soon he began to deteriorate rapidly. Fits occurred with greater frequency and many minor attacks, consisting only of momentary loss of consciousness, took place, and he was again admitted to hospital on May 2, 1910, in a completely inco-operative state, with a gross right hemiplegia and hemianæsthesia to pin-prick. There was a large left-sided temporo-sphenoidal hernia. Death took place thirteen days later.

Post-mortem examination.—The right temporo-sphenoidal lobe of the brain was enlarged and bulky, and seemed to compress the right optic nerve and the right side of the optic chiasma. On section a large circular reddish soft degenerate area was found in the anterior part of the right cerebral hemisphere, underlying the third right frontal convolution and the island of Reil. Also in the right temporo-sphenoidal lobe the cortical grey matter was not sharply differentiated from the underlying white matter, and in this area there were also a few scattered hæmorrhages. The anterior part of the corpus callosum and the fornix were somewhat enlarged, and the former presented a honeycombed appearance.

Microscopical examination.—This revealed that the naked eye changes were produced by a diffuse cellular overgrowth which involved not only the softened area of the right frontal lobe, but also spread throughout wide areas of the anterior parts of both hemispheres, and also the corpus callosum. It was composed of round, oval,

and elongated nuclei with granular chromatin network, resembling neuroglial nuclei, only somewhat denser. The nuclei varied very much in size and shape, and also in the density and manner of their arrangement in different areas (fig. 17). In the left parietal region the new growth was of fairly even density throughout the whole thickness of the cortex. Numerous well-preserved nerve cells were seen, but recognition of the cellular layers of the cortex was not possible. Mallory's phosphotungstic hæmatoxylin stain revealed neuroglial fibres, forming a dense network subpially and in the white matter, but the fibres were coarse and widely separated in the grey matter. Astrocytes and bipolar cells of varying size and form could be made out everywhere, but these formed only a small part of the actual new cell formation, which consisted mainly of smaller cells, the actual structure of which was not determined. A similar appearance was seen in the left temporo-sphenoidal lobe. In the inferior region of the frontal lobes the new growth was very dense, the nuclei more elongated and collected in parallel bundles in the subependymal region and under the pia. In the softened area of the right frontal lobe the nuclei were on the whole small and rounded and densely packed. Although it is not possible to present full pathological details of the case, the very clear clinical and pathological resemblance to Case 2 justifies its inclusion in this paper.

Summary of Case 3.

The case was characterized clinically by epilepsy, failure of memory, and symptoms of increased intracranial pressure which eventually proved fatal. Pathologically there was present a diffuse cellular overgrowth throughout wide areas of the anterior parts of the cerebral hemispheres. This was formed of astrocytic and spongioblastic cells, and was superimposed upon the essential nervous structures, gradually replacing them. The accompanying gliosis was not entirely irregular, but greater subpially and in the white matter, and less in the grey matter.

General Discussion.

The three cases which form the subject matter of this paper have been considered examples of a similar type of pathological change in the central nervous system. There are some differences in general histological appearance, especially between the first and second cases, but these appear to be differences in the rapidity of growth, and in the size and shape of similar types of cell, and not in the essential pathological process as is shown by the following considerations. In each case a widespread overgowth of cells of neuroglial origin with similar staining reactions had superimposed itself upon the essential nervous elements, and led to secondary changes in these structures in direct proportion to its intensity; so that one found all degrees of change, from a slight general increase of the normal neuroglia, to an area resembling a circumscribed new growth. This new growth was associated with a gliosis which varied with the normal struc-

ture of the nervous system, being a dense fine network in the white matter, and a coarse open network, staining faintly with victoria blue, in the grey matter of the cortex and basal ganglia. Also, there was in all cases dense fibril formation in those sites where there is normally a condensation of fibrous neuroglia, namely, in the outer zone of the molecular layer, underneath the ventricular surface, and along the blood-vessels. The clumping of newly-formed spongioblastic and astrocytic cells round the nerve cells was also found equally in the first two cases. Other similar features were the extension of the cellular and fibrous overgrowth into the leptomeninges and the walls of the blood-vessels, producing degeneration of the vessel walls and hæmorrhages round the vessels and into the superficial layers of the cortex. Hæmorrhages and fissuring in the gliosed tissue were also present in both cases in the deeper parts of the nervous system, the former being more marked in the first case, and the latter in the second.

With regard to the nature of the pathological process, it will be quite clear that the cases cannot be regarded as straightforward examples of tumour growth and an attempt made to classify them according to their possible cell of origin. In the first place the occurrence of characteristic cellular overgrowth underneath the pia on the undersurface of the cerebellum in Case 1, and the very great variation in the cellular overgrowth from point to point in Case 2, makes it unlikely that the growth could have arisen in any one area and spread directly as a single tumour formation. The tendency also for the overgrowth in the first case to involve mostly the cellular layers of the cortex and the subcortical white matter is an important point in this respect. Further, the retention of the normal elements of the nervous system, even in areas of severe new cell formation, is much greater than is found in true tumours of the nervous system. Apart from these considerations it would be impossible to designate as a tumour formation by direct spread, an overgrowth which varies its cellular and fibre overgrowth anatomically, so that one finds very constantly a sharp distinction at the junction of the subcortical white matter and the cellular layers of the cortex. This feature seems to indicate clearly, despite the very dense cellularity in some areas which would be quite indistinguishable if considered alone from an area of rapidly growing tumour formation, that the new formed cells had not escaped entirely from the laws that govern normal growth, and that their development was influenced to a much greater extent than is usual in simple tumour formation by the normal structures where the overgrowth was taking place.

Another unusual feature in the cases was the very great variation in the form and shape of the individual cells. In one area the section could easily be labelled medulloblastoma, in another spongioblastoma with fine

fibre formation or piloid astrocytoma, and in another diffuse astrocytoma. Any one, however, of these classifications of tumour growth would be quite inapplicable to the overgrowth as a whole. This varied appearance probably resulted from the differentiation of cells from immature to more mature forms to a much greater extent than takes place in a true neoplasm. Further, in the brain stem and cortical areas not involved in the general cellular overgrowth there were found abnormalities in the neuroglia which cannot be regarded as a direct spread of tumour growth throughout the nervous system.

This last observation seems to give a clue to the histogenesis of the whole overgrowth in that it probably indicates a developmental abnormality of the neuroglia generally, associated with which it is possible for the widespread cellular overgrowth to arise. The pathological process has therefore been regarded, not as a neoplasm in the strict sense of the term, but as a blastomatous malformation, in some way or other congenitally predetermined, although it is recognized that in reference to some parts of the overgrowth it may be impossible to define the boundaries between malformation and true tumour formation. This does not explain the origin of the new formed cells, whether from adult cells or from residual undifferentiated cells, nor the factors which caused the late onset of intense proliferation, but such questions are equally obscure in relation to the whole group of blastomatous malformations of the nervous system. If, however, some developmental abnormality of the neuroglia exists, it is possible that proliferative tendencies may develop in relation to this, and that a general overgrowth may arise over a widespread area, or having arisen in one area, cause its development in adjacent areas. On such a basis it is easier to understand the close relationship of the new formed cells to normal neuroglia and the gradual replacement of the nerve cells and fibres. The great capacity of the cells for differentiation, and also the variation of the cellular form and fibre development of the overgrowth depending on the surrounding tissues is more comprehensible.

It has been stated that general neurofibromatosis, affecting the peripheral nerves, is not a true neoplasm, but a diffuse fibroblastic overgrowth which may form focal manifestations resembling tumours, while in places true tumours may actually arise. The pathological process under discussion could be similarly regarded, the neuroglia in the nervous system being involved instead of the fibrous tissue in the peripheral nerves. Here, however, a much greater variety of pathological change is to be expected, because of the greater possibility of abnormal development in the neuroglia cells as compared with the fibroblastic cell.

Support for the conception that the cases under discussion are primarily

blastomatous malformations is found in the study of the central changes of Von Recklinghausen's disease. It is recognized that a feature of this disease is the occurrence, mostly in the cortex, of nests of gliogenous cells, or even a diffuse increase of glia which does not essentially disturb the cortex. Gamper (1929) described changes of this category in a case of Von Recklinghausen's disease, which showed also multiple ventricular and subependymal tumours. In the medial aspect of the frontal lobes anterior to the genu of the corpus callosum he found infiltrating both the cerebral cortex and white matter a diffuse cellular overgrowth which resembled in histological details very closely the changes found in the frontal region in the second case of this paper. This abnormality would be regarded as a blastomatous new formation of neuroglial cells in various stages of differentiation, and primarily dependent on some dysgenetic factor. Wherefore it seems reasonable to suppose that such an abnormality may in some cases be the predominant type of blastomatous change and spread widely over the cerebral hemispheres.

Another case may be mentioned. Schnyder (1928-29) has described in a thirty-one year old male, a dense gliosis of the right optic nerve with numerous glial cells, resulting in considerable demyelinization and thickening of the nerve. A diffuse glioma of the hypothalamus and neurofibromatous tumours on the 3rd cervical nerve and 9th intercostal nerve were also present. The intense gliosis of the optic nerve was very similar to the gliosis of the optic chiasma which was present in the first two cases of this paper. It is therefore significant that in the second case of this paper there were present skin changes such as are found in Von Recklinghausen's disease, and also a neurofibromatous tumour in the suprapituitary region, features which in themselves would justify one in regarding the widespread central changes as congenitally predetermined.

Correlation of the Cases with similar ones in the literature.

The similarity of the pathological changes found in the cases of Landau, Schwartz and Klauer, Hildebrandt, and Cassirer and Lewy especially with those in the second case of this paper, is very clear, and each of these authors regarded the pathological process as a widespread blastomatous overgrowth of neuroglial cells which had arisen in a congenitally abnormal tissue, or was dependent on a tendency to tumour formation affecting a wide area of the glial system.

Foerster's case is, however, more closely related to the first case of this paper, in that the distribution of the cellular overgrowth was very similar, and the cells were more elongated and rodshaped. The macroscopical

appearances of the cut brains were also similar. This case, however, showed no new formation of glial fibres, and no processes from the cells could be stained. Foerster therefore regarded the new formed cells as lemnoblasts, or precursors of sheath of Schwann cells, and called the disease central diffuse Schwannosis. It would appear very difficult to establish such a conception for a diffuse new growth throughout wide areas of the central nervous system. As the general characteristics of the pathological process in Foerster's case were very similar to Case 1 in this paper, it seems likely that the cells were really undifferentiated neuroglial cells, and that the case is similar to the group under consideration. This similarity is further evidenced by the presence of typical skin changes of Von Recklinghausen's disease in Foerster's case. The very early age of the onset of the disease may bear some relation to the undifferentiation of the cellular overgrowth.

In Santha's case, the child also was very young, being only 9 years of age. Santha also found some unipolar and bipolar spongioblast-like cells and a defective development of the macroglia. He regarded the main new growth, however, as composed of lemnoblasts; but, owing to the presence of spongioblast-like cells, stated that the lemnoblasts are in genetic relationship to the macroglia, and not to the oligodendroglia. It would seem more probable that the cellular overgrowth was in its entirety neuroglial, and that the pathological process is identical with that already discussed, but is nevertheless distinctive in that the new formed cells were for the most part undifferentiated abnormal glial cells.

It will be clear from the above discussion that one considers the cases of this paper, and those collected from the literature, as forming a distinct group, closely related pathologically, but with wide variations in microscopical details. The pathological relationship consists in a dysgenetic abnormality of the neuroglial system of the brain, whereby the tendency to a widespread blastomatous neuroglial malformation exists. The factors which will cause this to appear at one or other decade of life are unknown. The cases are primarily a blastomatous malformation, but in the areas of most dense overgrowth it may be impossible to say where malformation ends and true tumour formation begins. Gliomatosis cerebri seems the most suitable name for the entire group of cases. They are clearly closely related to Von Recklinghausen's disease, and appear analogous to the cases of widespread neurofibromatosis of the peripheral nerves, where the cellular overgrowth might be more correctly regarded as a blastomatous malformation than as a true tumour formation.

Relationship of Gliomatosis cerebri to other forms of Tumour Formation.

While the cases are thus closely related, on the one hand to the well-recognized group of blastomatous malformations to which the name of Von Recklinghausen's disease has been given, they are also related, on the other hand, to certain types of localized tumour formation in the central nervous system. These are glioma of the optic nerve, glioma of the pons or pontine hypertrophy, and diffuse glioma of the optic thalamus ; tumours which are very difficult to classify on any basis. Hudson, in 1912, recognised that tumours arising in the stem of the optic nerve were all of the same nature, and he classified them as degenerative gliomatosis of the optic nerve. Verhoeff (1932), although regarding them as true gliomas, did not attempt to classify them on an embryological basis. He noticed that the tumours did not advance by direct spread, but by causing the pre-existing neuroglia in the vicinity to proliferate. The tumours are composed of neuroglial cells, which vary from adult astrocytes to elongated spindle-shaped cells taking on the character, more or less, of spongioblasts. There is generally a variable formation of neuroglial fibres, and the tumour, in parts at any rate, is superimposed upon the actual structure of the nerve. These tumour formations are generally classified as polar spongioblastomas, but Russell and Bland (1934) have subjected one specimen to tissue culture, and found that stellar astrocytes were grown, so that they consider that the tumour should be designated piloid astrocytoma. This observation indicates clearly the tendency of the cells in the tumour to differentiate along normal lines. These are all features well exemplified in the cases of gliomatosis cerebri, and it seems possible that tumours of the optic nerve may be primarily a blastomatous malformation, dependent upon some congenital developmental anomaly, and cases have been described in association with Von Recklinghausen's disease. On such a basis the great variety of the histological picture may be better understood. Glioma of the pons and optic thalamus also show many features similar to those found in gliomatosis cerebri. The cells in the tumours are round, oval, and elongated cells clearly neuroglial in origin, with a tendency to grow in a very diffuse manner between the essential nervous elements, with special condensations underneath the pia, and sometimes, especially in the thalamus, around nerve cells. Classification of these tumours has been much discussed, and it is possible that again they may be dependent upon some congenital abnormality of the neuroglia with a greater tendency in these cases for the blastomatous malformation to be lost in true tumour growth. In the second case of gliomatosis cerebri in this paper, a minute focus of

true tumour growth having the characters of a spongioblastoma multiforme was found amidst the general cellular overgrowth. It is conceivable that cases might arise in which the picture was reversed, and large areas of tumour formation obscure the primary blastomatous malformation.

These suggestions with regard to the above-mentioned gliomas have been made because the patent similarities with the cases of gliomatosis cerebri indicated the possibility of a different angle of approach to their study. Further study of these tumours, however, and of the neuroglial system as a whole in such cases, may furnish information which will adequately explain their histogenesis, and in so doing throw further light on the cases of gliomatosis cerebri. A possible relationship also exists between the cases classified by Elvidge, Penfield and Cone (1937) as diffuse astrocytoma and gliomatosis cerebri because it seems inadequate to regard simply as a diffuse astrocytoma a pathological change which shows embryonic cells like spongioblasts differentiating into astrocytes, the retention of nerve cells in the midst of the tumour, and the accumulation of tumour cells around those nerve cells.

SUMMARY.

Three cases of diffuse cellular overgrowth of neuroglial cells throughout wide areas of the cerebral hemispheres have been described and correlated with other cases from the literature. The name gliomatosis cerebri has been considered most suitable for cases of this type, and they have been regarded pathologically as primarily blastomatous malformations arising upon a congenital developmental defect, although it is clearly recognized that it may be impossible to say where malformation ends and true tumour formation begins. Clinically, the cases were characterized by a long history of epilepsy, followed by mental symptoms, especially failure of memory and character changes and symptoms of increased intracranial pressure. Symptoms of focal disease in the brain were absent or late. The relation of the cases to certain localized tumour formations in the nervous system has been discussed.

This work was carried out during the tenure of the Pinsent Darwin Studentship in Mental Pathology.

I wish to thank the Physicians who have allowed me to publish their cases. My thanks are also due to Professor Pulvertaft for permission to take the photomicrographs; and to Dr. Denny Brown for photomicrographs 15 and 17. I also wish to thank Dr. Greenfield for his criticism and advice.

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LEGENDS FOR PLATES V, VI, VII.

FIG. 2. *Case 1.*—Camera lucida drawing from preparations stained by Hortega's silver carbonate method for astrocytes. (*a*) Examples of the cell types found in the thalamus. (*b*) Cellular layers of the cortex showing the varied size and shape of the new formed cells. Those round the nerve cells are astrocytes and spongioblasts. (*c*) Molecular layer of the cortex showing the marginal bundles of piloid fibres and bipolar cells, and also the predominance of astrocytes in the deeper parts of the layer.

FIG. 3.—*Case 1.*—Perivascular overgrowth displacing the myelinated fibres in the thalamus. Spielmeyer's myelin stain counterstained with carmine.

FIG. 4. *Case 1.*—Fibrillar bundles of cellular overgrowth along the cortical margin. Iron hæmatoxylin and van Gieson.

FIG. 5. *Case 1.*—Dense cellularity running along a blood-vessel into the cortex. The surrounding cortical infiltration is moderately severe. Nissl.

FIG. 6. *Case 1.*—Severe overgrowth in the cellular layers of the cortex, with distortion of the remaining nerve cells. Nissl.

FIG. 7. *Case 1.*—Dense subpial cellular overgrowth along both sides of a cerebral fissure. Iron hæmatoxylin and van Gieson.

FIG. 8. *Case 1.*—Subpial infiltration in the cerebellum. Iron hæmatoxylin and van Gieson.

FIG. 12. *Case 2.*—Severe cellular overgrowth in the cellular layers of the cortex. One or two nerve cells remain, and there is calcification in relation to a vessel. Iron hæmatoxylin and van Gieson.

FIG. 13. *Case 2.*—Same region as fig. 12. Bundles of neuroglial fibres running along small blood-vessels. The coarse neuroglial fibres in the background are only faintly stained. Anderson's victoria blue.

FIG. 14. *Case 2.*—Dense gliosis in the subcortical white matter. Anderson's victoria blue.

FIG. 15. *Case 2.*—Moderately severe cellular infiltration of the cortex showing clumping round nerve cells and the arrangement of the new formed cells in short chains. Iron hæmatoxylin and van Gieson.

FIG. 16. *Case 2.*—Focus of anaplastic tumour formation in the left frontal lobe. Davenport's stain.

FIG. 17. *Case 3.*—Severe cellular infiltration in the cortex showing residual nerve cells. Iron hæmatoxylin and van Gieson.

SUBACUTE DIFFUSE EPENDYMITIS.

BY R. M. STEWART.

It is possible to recognize three forms of ependymitis, the acute, the subacute, and the chronic. Of these the first named is a comparatively common condition, being in most cases either merely the extension of a purulent leptomeningitis to the ventricles of the brain, or, as in meningococcal meningitis, part of a septicæmia in which the organisms reach the ventriculo-subarachnoid system not by way of the meninges, but through the choroid plexus. In those instances in which the patients survive the acute phase of their illness this type of ependymitis, by closing the avenues of escape for the cerebrospinal fluid, may produce internal hydrocephalus as an end-result.

Chronic ependymitis is of an altogether different character. For example, the so-called granular ependymitis characteristic of parenchymatous syphilis owes its development more to a subependymal glial overgrowth than to an actual hyperplasia of the ependymal lining and its presence is but one indication of a widespread proliferative gliosis which spares no part of the nervous system.

On the other hand, subacute ependymitis differs from the other two forms in that it is capable of arising as an isolated and primary inflammation of the entire ventricular system, strictly limited to this system, with no concomitant inflammation in the subarachnoid space.

As in the case now reported the clinical features to which the condition gives rise may be puzzling and are often suggestive either of posterior fossa neoplasms or suprasellar tumours.

Case Report.

History.—E. H., aged 56, single, was admitted to Leavesden Hospital on December 5, 1933, in a condition of secondary dementia. She had been feeble-minded all her life and from April, 1926, to December, 1933, was a patient in Bexley Hospital, the clinical history being one of depression, agitation, delusions of persecution and hallucinations of hearing.

State on Examination, December 5, 1933.—The patient was very obese. Height 4 ft. 10 in., weight 14 st. 9 lb. Her articulation, pupils and cranial nerves were normal, but her gait was feeble and unsteady and pain in the back was a prominent symptom.

Progress.—Three weeks after admission tremor of the right hand was noticed and pain was now complained of in the arms. In June, 1934, six months after admission, she had become even stouter, walking was more difficult and the tremor of the right hand more pronounced. Her urine was free from sugar and a sugar tolerance test gave the following readings:—

0	hr. =	125	mg.	per	100 c.c.
½	hr. =	187	„	„	„ „
1	hr. =	227	„	„	„ „
1½	hrs. =	186	„	„	„ „
2	hrs. =	173	„	„	„ „

Serum calcium 10·7 mg. per 100 c.c. Serum phosphorus 4·6 mg. per 100 c.c. Blood-pressure 150/60.

Roentgenographic examination of the skull negative. Normal pupillary reactions continued to be obtained and the fundi showed no abnormality.

In December, 1934, twelve months after admission, the patient appeared to be in failing health ; the heart sounds were feeble, cyanosis was present and patches of pigmentation, first noticed in July, had become much more marked, especially in the axillæ, groins, and round the umbilicus. The patient was emotional, crying incessantly, salivating and dribbling. There was no pyrexia.

In January, 1935, the conjunctivæ and skin acquired an icteric tinge and for the first time involvement of the cranial nerves was detected. The pupils, equal in size, reacted sluggishly to light and on accommodation-convergence ; a left external strabismus and right-sided facial paresis were noted. The face was expressionless and this, coupled with tremor of the fingers of the cigarette rolling type, gave the patient an appearance somewhat suggestive of Parkinsonism. The lower limbs showed no tremor or rigidity and all deep reflexes were brisk. The patient was still able to leave her bed and sit in a chair for short periods.

In April, 1935, sixteen months after admission, remittent fever of a mild grade, which never exceeded 101° F. was recorded. The jaundice and cyanosis were more marked, the left border of the heart was displaced outwards and the patient had become considerably less obese, the reduction in weight amounting to 3 st. Vomiting occurred at infrequent intervals. Tremor of the fingers was still present and both upper limbs were somewhat rigid. The plantar reflexes were normal, the arm-jerks brisk, the knee and ankle jerks absent. Pain in the arms and shoulders was a prominent feature, and with increasing cyanosis and dyspnœa the patient became drowsy and gradually weaker. Several days before death small purpuric spots appeared on the abdomen and legs. Death occurred on May 26, eighteen months after the onset of symptoms.

Post-mortem examination.—An autopsy was held fourteen hours after death. The body was that of an extremely obese adult female, the distribution of fat affecting the shoulder girdles, upper limbs, breasts, abdomen, thighs, and buttocks. There was a noticeable degree of dark pigmentation of the breasts and groins. The fingers showed a slight degree of clubbing. The thyroid gland was normal, the lungs showed basal congestion and the heart considerable enlargement, weighing 360 grm. The left ventricle showed hypertrophy, the right ventricle dilatation. The coronary arteries showed a moderate degree of atheroma, but on the whole the myocardium was fairly healthy. On the mitral surface of each of the three

aortic valve cusps there were numerous small vegetations of a red colour. These were not firmly attached and there was no ulceration of the valve segments. The remaining valves were healthy. The liver—1,055 grm.—showed a moderate degree of fatty infiltration; the spleen was moderately enlarged, soft and friable. The kidneys showed no gross changes. The lower end of the ileum, the cæcum and the first two feet of the ascending colon were gangrenous, owing to an embolic blockage of a branch of the superior mesenteric artery.

Nervous system.—The calvarium and dura mater were slightly thickened. The brain weighed 1,350 grm., and it was evident that a considerable degree of internal hydrocephalus was present. On removal of the brain the pituitary gland was seen to be markedly compressed. Except in the interpeduncular fossa and in the

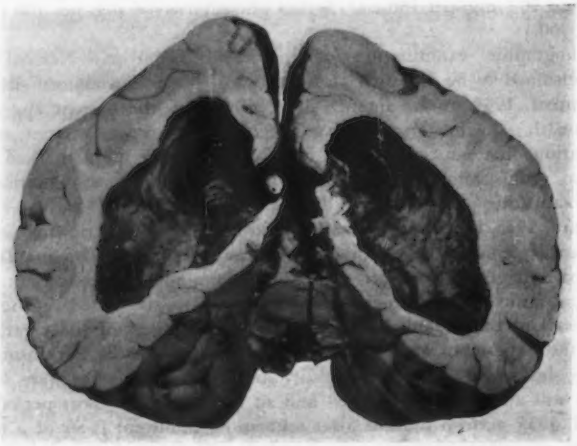

FIG. 1.—Vertical coronal section of cerebral hemispheres to show ependymitis of the greatly dilated anterior horns of the lateral ventricles. 5/8 actual size.

neighbourhood of the Sylvian fissures the pia-arachnoid was quite normal; in these situations the pia was slightly thickened but there was no evidence of exudate; at the base the arteries showed a moderate degree of atheroma. Some flattening of the fronto-parietal convolutions was present, otherwise they were of normal configuration. The cerebral hemispheres after ten days' immersion in formol saline were divided and weighed: right cerebral hemisphere, 485 grm.; left cerebral hemisphere 490 grm.; cerebellum and brain-stem 149 grm. The most obvious feature was the extreme degree of ventricular dilatation, more marked on the left side and affecting equally the body and horns of the lateral ventricle. The septum lucidum was thickened and the corpus callosum thinned and stretched. Both foramina of Monro were dilated and the 3rd ventricle markedly distended, its floor bulging downwards in a caudad direction. The 4th ventricle did not share in the dilatation (fig. 1). The cerebrospinal fluid which escaped from the ventricular system was clear and limpid.

PLATE VIII.

FIG. 2.

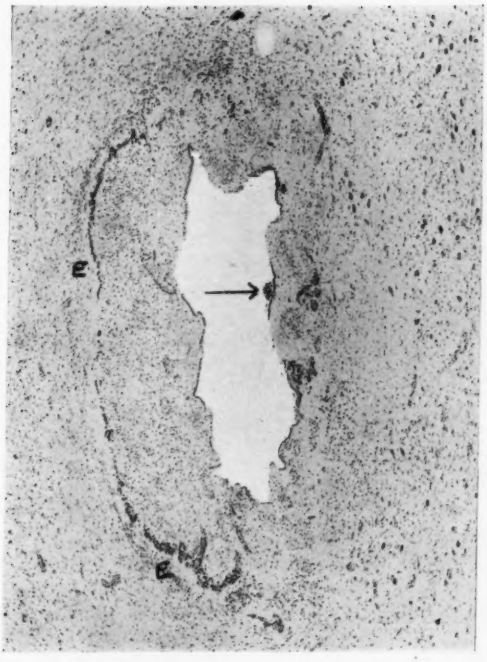

FIG. 3.

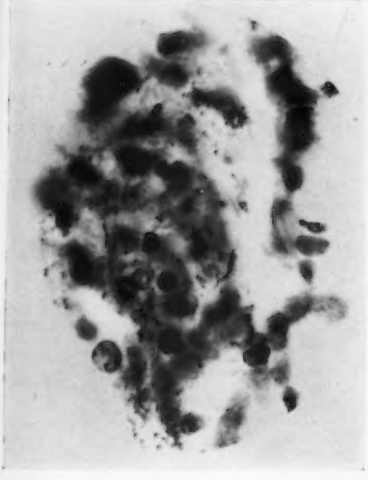

FIG. 4.

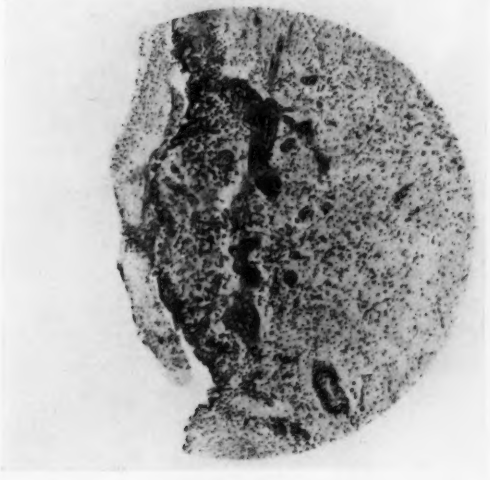

FIG. 5.

To illustrate paper by R. M. Stewart.

The ventricular walls presented a most unusual appearance. Instead of the smooth glistening surface the ependyma was rough, uneven and peppered all over with dark hæmorrhagic spots, many of the size of a pin's head. With a hand lens it could be seen that the ventricular lining had a decidedly granular appearance. These changes were most marked on the outer walls of the anterior horns, on the mesial walls of the occipital horns and on the walls of the 3rd ventricle. The inflammatory process also extended to the floor of the 4th ventricle where the ependymitis was so marked as to conceal the normal outlines of anatomical areas.

The choroid plexus did not appear flattened or bound down by inflammatory exudate.

At its commencement the aqueduct of Sylvius was slightly dilated but at its lower end it narrowed gradually until about 1 mm. above its termination it appeared to be almost completely occluded.

Microscopic appearances.—The pia-arachnoid investing the cerebral hemispheres showed no evidence of inflammation but some thickening and œdema were present in the neighbourhood of the Sylvian fissures.

In the cortical grey matter singularly few changes of an inflammatory character were present ; in particular there was no evidence of perivascular infiltration, and no pyæmic foci were found ; the glial components showed slight reaction. The cyto-architectonics were undisturbed although the larger nerve cells showed chromatolytic changes of a rather acute character. The " verödungsherde " characteristic of bacterial endocarditis were not found. The underlying white matter and the basal ganglia also participated in this relative freedom from inflammatory phenomena, but near the ventricular walls inflammatory changes were present in the brain substance and these became more pronounced as the free ependymal surface was approached. Many of the blood-vessels in this neighbourhood showed small-celled perivascular infiltration and nearly all contained masses of polymorphs in their interior. Organisms, however, could not be found either in or around the vessels.

Glial reaction was present both in the neighbourhood of these vessels and in the subependymal region. Numerous astrocytes, oligodendroglia and " gemastete " cells were present in the peri-ependymal region, and in the same locality small hæmorrhages occurred in large numbers (fig. 2).

On some parts of the ventricular wall the cells of the ependyma were intact and retained their cuboidal shape, in other situations they had entirely disappeared, or had proliferated and lay under a fibrinous exudate in which were lymphocytes, polymorphonuclear cells, fibroblasts and plasma cells, the latter in small numbers. Clumps and short chains of cocci, often forming solid masses, could be seen lying in the inflammatory exudate on the walls of the lateral ventricles and also in situations where there was little evidence of inflammation ; although they were present throughout the ventricular system nowhere else were they found in such large numbers.

The inflammatory changes described above were also very marked in the walls of the 3rd ventricle but the outer walls of the descending horns of the lateral ventricles were singularly free from evidence of inflammation though organisms could be seen lying on the free surface of the ependyma in this situation.

In the region of the aqueduct of Sylvius important changes were present. The ependymal cells had undergone proliferation but very irregularly, so that side by side with ependymal granule or hillock formation there were areas in which

their arrangement was quite undisturbed. Towards its lower end the aqueduct was partially closed by a productive inflammatory process in the fibrous meshwork of which nests of ependymal cells could be discerned. Under a high power, chains and clumps of cocci could be seen lying in the midst of inflammatory cells but no organisms were found in the deeper layers of the peri-aqueductal grey matter. Complete closure of the iter had not occurred though its lumen was much encroached on and at one point separated up into several small canals (figs. 3 and 4).

Equally striking was the very marked degree of subependymal gliosis which became more pronounced at the lower end of the canal. On the floor of the 4th ventricle it formed a dense felt-like mat overlaid by proliferating ependymal and inflammatory cells lying among which were numerous organisms (fig. 5). In addition to the fibrous glia the peri-aqueductal grey matter contained swollen glial cells and nerve cells which exhibited acute degenerative changes. In this locality, too, some of the blood-vessels showed hyaline degeneration of their walls. Small hæmorrhages were also found in the subependymal region of both the pons and medulla. In the same localities endovascular leucocytic clumping was conspicuous but no organisms were found in the interior of vessels.

Many of the nerve cells of the pons were heavily pigmented.

The spinal cord showed a moderate glial increase of the astrocytic type but the vessels showed no perivascular infiltration. The central canal was closed. On the other hand, the investing pia-arachnoid was thickened and showed a pronounced inflammatory reaction, the condition being in fact a leptomeningitis of a rather acute character. For the most part the exudate consisted of polymorphs, lymphocytes and mononuclear phagocytes and a small amount of fibrin. Lying among the inflammatory cells were numerous Gram-positive cocci, often arranged in short chains.

The choroid plexus.—Both in the lateral and 4th ventricles the choroid plexus showed little evidence of inflammatory reaction, it being impossible to say that any marked degree of choroiditis existed. Some œdema and vascular dilatation was present but on the whole the tuft cells were singularly free from degenerative or inflammatory changes.

Discussion

In the absence of any widespread inflammatory reaction either in the cerebral cortex or of its membranes it is evident that we are here dealing with an example of the relatively uncommon form of ependymitis for which the term primary is justifiably employed. In this type the inflammatory process is strictly limited to the ependymal lining of the intraventricular system of the brain and the symptoms to which it gives rise are largely those of an obstructive hydrocephalus secondary to closure of the ventricular foramina. With regard to the ætiology of these cases little is known.

In a case of acute ependymitis to which the patient succumbed within forty-eight hours, Coutts (1903) isolated streptococci from the ventricular fluid, but no infection was found in the other organs. In a closely analogous case in which Fisher (1903) reported the co-existence of acute

ependymitis with lobar pneumonia, Friedländer's diplobacillus was present in the ventricular fluid as well as in the lung tissue. But in the subacute type direct evidence of infection is almost always lacking and for an explanation of the strict limitation of the inflammatory process to the ventricular system it is necessary to assume the presence of an abnormal permeability of the blood-brain barrier which permits bacteria or toxins to pass from the circulation through the choroid plexus to the cerebrospinal fluid. In recent years several striking examples of subacute ependymitis have been reported. In the case reported by Globus and Strauss (1928) the illness, which was marked by remissions and exacerbations, lasted ten months; symptoms suggestive of tumour of the 3rd ventricle were observed, and ventriculography revealed an obstruction of both foramina of Monro. At the autopsy a subacute inflammatory process involving the entire ventricular system was found. In the 3rd ventricle the ependyma and subependyma had separated from the wall of the cavity to form a pseudo-cyst which partly blocked the aqueduct of Sylvius. Careful search failed to reveal any evidence of inflammatory reaction in the choroid plexus nor were the mild degenerative and inflammatory changes seen in the adjacent brain tissue anything more than a reaction to a contiguous inflammatory process. In the widespread ependymitis there were present all gradations from the mildly acute purulent in the lateral ventricle to the chronic granular ependymitis in the aqueduct and 4th ventricle.

On the basis of these findings the authors suggested that at least some instances of chronic granular ependymitis have their beginnings in mild and slowly progressive acute forms.

Other accounts of this condition have been recorded by Merle (1910), Tillgren, Spiller (1902), Cushing (1903), and Arnold, Jr. (1934).

In the case of Arnold the similarity of the pathological findings to those described by Globus and Strauss was striking. The patient's illness lasted little more than two months and the outstanding symptoms were those of mental deterioration and headache. The neurological signs were bilateral and of little localizing value. Ventriculography showed symmetrical dilatation of both lateral ventricles, the other ventricles being of normal size. No organisms were found in the cerebrospinal fluid withdrawn from the lateral ventricles. The pathological changes consisted of obstruction of the foramina of Monro by a subacute inflammatory process; there were present a marked glial reaction, destruction of the ependymal lining, swelling and hyperplasia of the choroid plexus, a marked perivascular lymphocytic reaction involving the subependymal tissues of

the entire ventricular system and the presence in many places of isolated ependymal granulations. There was no evidence of visceral syphilis and bacteria were not found. Though not normal the cerebral aqueduct was not obstructed.

It will be observed that in both of these two cases closure of the foramina of Monro played a major part in determining distension of the lateral ventricles, but obstruction of the Sylvian aqueduct by itself must be reckoned almost as common as a cause of internal hydrocephalus; in such cases the 3rd ventricle will naturally participate in the distension, while the 4th ventricle retains its normal size and shape.

Of this type of occlusion there have been numerous reports but it is noteworthy that few, if any, of these can be regarded as instances of subacute ependymitis, peri-aqueductal tumours and simple hyperplasia being commoner causes of obstruction. Usually, too, the changes are of a chronic character, the brunt of the damage falling on the peri-aqueductal tissue which becomes the seat of a fibrous glial proliferation with but slight involvement of the overlying ependyma. Evidence of inflammation is, indeed, often conspicuous by its absence, and perhaps for this reason the view has been advanced that not a few of the proliferative cases are of developmental origin. It has been suggested by Spiller (1916) that the process of aqueductal narrowing which takes place late in fœtal life may proceed beyond the normal limits with a resultant hydrocephalus of the obstructive type at some period of postnatal life. According to this hypothesis the process is somewhat analogous to that which may occur under supposedly normal conditions around the central canal of the cord. But, as Stookey and Scarff point out, anatomical considerations lend no support for this analogy for the mechanism operative in closure of the spinal canal is different from that for the Sylvian aqueduct. In the former, simple fusion of the neural groove is followed by an obliterative process which spares only the most ventral part of the primitive central canal, whereas, in the aqueduct of Sylvius the primitive central canal is not obliterated, but merely undergoes modifications of shape and size owing to the encroachment on it of surrounding anatomical structures. The hypothesis of a developmental origin has also been contested by Dandy (1920) who postulates the intervention of some toxic, inflammatory or traumatic process occurring before or after birth and which, by injuring the aqueductal lining, brings about a secondary glial overgrowth and finally stenosis.

Cases of occlusion of the aqueduct by a diffuse inflammatory process involving almost the whole ventricular lining have been reported by

Sheldon, Parker, Kernohan (1930) and by Orton (1931). The appearances in the two cases recorded by Sheldon and his co-workers were dissimilar. In the first the condition was visible to the naked eye as a thick, gelatinous exudate covering the surface of the lateral and 3rd ventricles; on microscopic examination this was seen to consist of masses of chronic inflammatory cells. In the second case there was diffuse granular proliferation of the subependymal tissues and instead of a smooth exudate there were visible innumerable small granules, constituting the so-called granular ependymitis. In neither case was it possible to ascertain how the infection was acquired nor by what pathways it had entered the ventricular system. It must, however, be noted that both these cases belonged to the chronic rather than to the subacute type, the duration of the illness being two and four years respectively. But even in the subacute type where pericanalicular gliosis is less conspicuous than the ependymal involvement and where there is often clear indication of an inflammatory origin in the adjacent perivascular spaces, the actual cause usually remains obscure.

From this aspect the case now reported is exceptional for not only was there abundant evidence of inflammation in the subependymal tissues but no difficulty was experienced in demonstrating the presence of large numbers of micrococci in the fibrinous exudate on the walls of the ventricular cavity. Though unfortunately the identification of these organisms by culture was not attempted it can hardly be doubted that they were derived from the bacterial endocarditis to which the patient succumbed. Concerning this disease, it may be recalled that it usually presents a fairly definite symptomatology. The insidious onset, the variable fever, the brownish pigmentation of the skin, dyspnœa, progressive cardiac failure, clubbing of the fingers and embolic phenomena form a composite clinical picture which can hardly escape recognition. It was reproduced with great fidelity in this patient though whether it was caused by the *Streptococcus viridans*—the organism most frequently found in subacute endocarditis — must remain undecided. The presence of organisms flourishing in enormous numbers on the endocardial surface of the heart with little or no response from phagocytic cells is a striking peculiarity of bacterial endocarditis and in this case was illustrated by masses of organisms lying on the ventricular surface with no accompanying invasion by polymorphs.

Concerning the mode of infection of the ventricular system it is not possible to speak with any degree of certainty. It seems obvious, however, that the cerebrospinal fluid in the ventricles was not infected from without, that is to say from the meninges, since no organisms and no evidence

of inflammation were present in the pia-arachnoid, save in one situation —the upper cervical region of the cord—and in this area the acuteness of the inflammatory process spoke in favour of a terminal stage of meningitis attributable to the escape of organisms through the roof of the 4th ventricle.

In a disease such as subacute endocarditis in which organisms are widely disseminated through the blood-stream, infection of the brain tissues is to be expected, and has, indeed, been frequently reported, notably by Kimmelstiel, who found aneurysms, vascular thrombosis, ischæmic foci and multiple inflammatory areas in the cerebrum. Consequently the likelihood of infection of the cerebrospinal fluid from the blood-stream must be entertained. In the case under discussion no changes of the widespread character described by Kimmelstiel were found, evidence of inflammatory reaction being limited to the neighbourhood of the ventricular walls. No thrombosed vessels or ischæmic foci were seen and the possibility of infection from this region is purely presumptive.

Certain writers have claimed that organisms can reach the ventriculo-subarachnoid system not by way of the meninges but through the choroid plexus and obviously the presence in this situation of a metastatic focus would afford a direct route for invasion of the cerebrospinal fluid. In one of their two cases of diffuse inflammatory ependymitis, Sheldon and his co-workers found in the choroid plexus of the lateral and 3rd ventricles lymphocytes, polymorphs and small thrombosed vessels so that notwithstanding the negative character of the histological appearances in the case under discussion the possibility of a mechanism of this sort must be given serious consideration.

In this case the degree of proliferative gliosis which accompanied the ependymitis was so marked, especially in the pons and medulla as to raise the question of whether the gliosis may not have preceded the involvement of the ependyma, the organismal invasion being thus a secondary phenomenon attacking an already diseased system and, perhaps, limited in time to the last few weeks of the patient's illness.

As already mentioned, alternative hypotheses have been advanced in explanation of aqueductal stenosis of long standing; of these the first postulates an involutional or developmental hyperplasia of the sub-ependymal glia, the second holds that the proliferative changes in the glia are secondary to some previous inflammatory process that has resolved, leaving no vestige of the original infection which brought them into being. For the first view there is something to be said when the patient succumbs at a comparatively early age, as in the cases recorded by Spiller

(1902) and Dijkstra (1930) or when, as in Orton's case (1931), the patient has a hydrocephalic type of cranium indicating that imperfect drainage of ventricular cerebrospinal fluid must have been present at an age when growth of bones of the skull was still active, but in the case now reported the patient showed no enlargement of the head and since she had attained her fifty-sixth year, a developmental gliosis commencing at so late a period of life would be most unlikely. On the other hand, the duration of her illness and the whole clinical history were quite compatible with the presence of an infective ependymitis pursuing a comparatively slow and insidious course and since evidence was not lacking of reactive phenomena of fairly long standing beneath the ependyma it may legitimately be concluded that the lowness of the virulence which confers on bacterial endocarditis lenta its subacute character was in this case responsible for the changes produced in the ventricular walls and in the aqueduct of Sylvius.

Finally, it may be remarked that, as in this case, complete closure of the aqueduct of Sylvius is not necessary for the establishment of a progressive ventricular dilatation. This channel is normally so minute that even a moderate encroachment on its lumen seems to be sufficient to determine an obstructive hydrocephalus.

From the diagnostic standpoint it was unfortunate that efforts to obtain a sample of cerebrospinal fluid were unsuccessful, for the presence of organisms in the fluid would have afforded a clue to the nature of the condition. Without this diagnostic aid the patient's symptoms—mental deterioration, change of personality, headache, vomiting, muscular rigidity and tremor, cutaneous pigmentation and increasing obesity—were misleading and were indeed interpreted as evidence of an intracranial neoplasm with probable involvement of the pituitary body. This simulation of intracranial tumour in subacute ependymitis has been noted by a number of other writers and it is clear from accounts in the literature that even when all diagnostic aids, including ventriculography, are employed, occasionally the actual cause of the internal hydrocephalus can only be determined by an exploratory operation.

Summary.

A feebleminded woman, aged 56, succumbed to bacterial endocarditis of eighteen months' duration. Examination of the nervous system showed the presence of a subacute ependymitis of the lateral 3rd and 4th ventricles; associated with this there was a partial stenosis of the aqueduct of Sylvius which had produced a marked degree of internal hydrocephalus. Inflammatory changes were limited to the ependymal and subependymal

regions of the brain and except for the presence of a leptomeningitis in the upper cervical region of the cord, the pia-arachnoid was free from evidence of inflammation. Large numbers of micro-organisms were present among inflammatory cells lying on the surface of the ependymal lining of the ventricles. A marked proliferation of the subependymal glia accompanied these changes.

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LEGENDS FOR PLATE VIII.

FIG. 2.—Wall of 3rd ventricle. Note the irregular ependymal surface and the presence of free hæmorrhages in the subependymal tissue. Mallory's stain. × 50.

FIG. 3.—Lower end of aqueduct of Sylvius showing partial stenosis. Note submerged ependymal cells E. Arrow points to a clump of polymorphs containing many cocci. Cresyl violet stain. × 34.

FIG. 4.—High-power view of the clump of polymorphs indicated in fig. 3. The organisms are streptococci arranged in short chains. × 600.

FIG. 5.—Floor of 4th ventricle showing intense gliosis. The ependymal cells are still present. Cresyl violet. × 38.

THE CENTRAL PATHWAY IN MAN OF THE VASOMOTOR RESPONSE TO PAIN.[1]

BY D. G. MARQUIS AND D. J. WILLIAMS.

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INTRODUCTION.

LITTLE is known of the intramedullary pathways governing the activity of the sympathetic nervous system in man. Clinical and experimental observation have given rise to speculation concerning "centres" in the cerebral cortex, the hypothalamus or the medulla, and to conjecture as to the tracts below this level. The issues cannot be completely settled by animal experimentation, for the results are frequently at variance from one species to another, and in some points are in clear disagreement with the results obtained from the study of man.

Since the peripheral sensory nerves are known to be the afferents for sympathetic response as well as for somatic sensation, it may be possible to study the relation of the intramedullary pathways involved in sensory perception to those used by the sympathetic response. At those points in the central nervous system where the two pathways are identical, any pathological lesion resulting in sensory changes should likewise result in corresponding changes in the sympathetic responses to the stimuli. Conversely, where the two pathways are not identical, there should be a dissociation of the sensory changes and the sympathetic responses.

Accordingly, a series of patients with lesions of the nervous system at various levels from peripheral nerve to cortex were selected for study. The patients all presented marked sensory changes, either a decrease or an

[1] Work undertaken in the Research Unit, The National Hospital, Queen Square, London, under the tenure by Dr. Marquis of a Rockefeller Travelling Fellowship, and by Dr. Williams of a Halley Stewart Research Fellowship.

increase in the intensity of the subjective appreciation of peripheral stimulation. The sympathetic response selected for measurement was the vasoconstrictor response recorded with a finger plethysmograph.

We wish to thank those members of the Staff of the National Hospital, Queen Square, who allowed us to study their patients in this investigation, and those normal subjects who served as controls. We wish also to thank Dr. J. Doupe for his help in some of the experimental procedures, and Dr. Carmichael for his valuable advice and criticism.

Method.

The technique used in recording vasomotor responses has been described in detail elsewhere (Bolton, Carmichael and Stürup, 1936). A small glass plethysmograph was placed on a finger or toe and sealed with zinc oxide paste. The plethysmograph was connected by pressure tubing to a tambour on which was mounted a mirror which reflected a beam of light to the slit of a continuous film camera. The optical magnification provided a recorded excursion of approximately 1 mm. per 10 c.mm. of finger volume change. (*see* fig. 1).

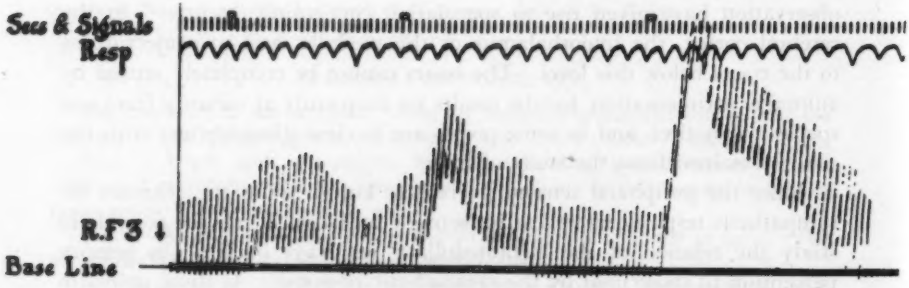

Fig. 1.—The vasoconstrictor responses to equal stimuli on skin areas of differing sensitivity. The volume of the right middle finger and the respiratory phases of Case 1 are recorded. The record reads from left to right, the arrow points in the direction of an increase in finger volume, and time is recorded in seconds. At the first signal a single pin-prick was made in the hypalgesic area, causing a deflection of 5 mm., at the second a similar prick on the normal skin caused 15 mm. deflection, and at the third the same stimulus on the hyperalgesic area caused a deflection of 33 mm. of the recording beam of light.

The sensory stimuli employed to evoke the vasomotor responses were carefully calibrated and standardized to ensure the objective equality of stimuli applied to normal and affected regions of the body. The pin-prick stimulus was delivered by means of a modified Head algesiometer, with which the intensity could be varied by adding or removing weights. After

preliminary experiment two intensities were selected for subsequent work. These have been designated as "weak" and "strong" pin-prick. The former was normally perceived as sharp but not unpleasant; the latter was definitely painful and when applied without warning was apt to provoke retraction of the part stimulated.

Pressure stimulation was applied with a calibrated spring instrument which indicated pressures of 1 to 10 kg. The contact surface was a rounded bakelite button 1 cm. in diameter.

Temperature stimuli were obtained by the application of flat-bottomed copper calorimeters, 5 cm. in diameter, which were filled with water of measured temperature. Stimuli designated as "hot" were between 45° and 50° C.; the "cold" stimuli were between 0° and 10° C.

Stimuli were applied to the patient in a predetermined random order at various points on the body in order to avoid any marked adaptation effects. Sufficient time elapsd between stimuli for the return to the basic dilated state. Note was made of any verbal or expressive indications of the painfulness of the stimuli, and at one or more times during the experiment the patient was asked to compare systematically the sensory qualities of the stimuli on the normal and affected parts of the body.

Since previous experiments in this laboratory have shown that the response to sensory stimulation is invariably in the direction of vasoconstriction, records were taken only when the skin vessels were maximally dilated. This provided a constant background condition for all cases, upon which the vasoconstrictor response was clear and definite. The dilatation was brought about in most instances by immersion of both legs in a water bath at about 43° C.

In some cases plethysmographic records were obtained from a finger of both the right and left hands, but in no instance was any constant difference between the magnitude of the responses on the two sides noted. The results, therefore, are reported for one digit only. This was usually the one on the unaffected side of the body, since the record was less disturbed by tremors or involuntary movements.

Simultaneous photographic records of the respiratory movements of the thorax were made in order to identify and eliminate from consideration those vasoconstrictor responses which follow deep inspiration.

Five normal young post-graduate students and twenty-three patients with focal lesions of the nervous system involving sensory pathways were examined. The abnormal patients were chosen with predetermined criteria in view. Their lesions were clinically well localized and in four were verified at operation. They had definite subjective sensory changes, were co-operative, and had normally responsive peripheral vascular beds.

Eight of the twenty-three patients failed to meet all of these criteria and were therefore discarded from the experimental series. In order adequately to compare the results obtained in patients with a "thalamic syndrome" an attempt was made to obtain some subjects with hyperalgesia as well as those with hypalgesia.

Observations.

To evaluate the results obtained from the patients with various lesions of the nervous system it was necessary to demonstrate in normal subjects that stimuli on the right and left sides of the body were equally effective in eliciting vasoconstrictor responses. Table I presents a summary of the data obtained from studies of the normal control group with various types of stimulation.

TABLE I.

Comparison of the vasoconstrictor responses in normal subjects to stimuli on the two sides of the body. Each value represents the mean of from 10 to 20 responses, expressed in millimetres of deflection. The columns headed "t" and "P" represent the statistical significance of the difference as explained in the text.

Subject	Stimulus	Right	Left	Difference	t	P
1	Strong PP *	14·9	15·0	0·1	0·035	0·9
	Cold	23·0	24·1	1·1	0·196	0·8
2	Cold	36·7	37·7	1·0	0·157	0·8
3	Strong PP	27·2	32·0	4·8	0·869	0·3
	Cold	40·3	43·9	3·6	0·526	0·6
4	Strong PP	14·9	14·2	0·7	0·215	0·8
5	Strong PP	32·6	30·4	2·2	0·325	0·7
	Cold	22·8	21·4	1·4	0·269	0·7

* Pin-prick.

Although the variability of vasoconstrictor responses was too great to permit comparison of single measurements, the average values for ten or more stimuli showed a striking correspondence between the two sides of the body. Consequently, all values reported in this study are means of from ten to twenty individual measurements.

The statistical significance of the differences between means was computed by Fisher's (1932) method for small samples. The ratio of the differences to the estimated standard error of that difference is called t, and from appropriate tables the probability (P) of the observed difference arising by chance is determined. When P is less than 0·02 (which signifies that the difference in question might be expected to occur fewer than twice in 100 samples drawn at random from a homo-

geneous population) the difference may be regarded as significant. It will be seen in Table I that none of the differences is large enough to be considered as anything but chance differences. It was also apparent that there were large differences between individuals in the magnitude of the responses to similar stimuli but since the problem of this study demands comparisons of one region of the body with another in the same person, the factor of individual differences does not enter into the results.

Preliminary investigation also demonstrated that there was a correspondence in normal subjects between the size of the vasoconstrictor response and the objective intensity of the stimulus. With increased severity of stimulation, and therefore greater subjective sensory intensity, the objective vasoconstrictor response was also increased. This may be illustrated by reference to Cases 3, 4, 12 and 15, with whom different intensities of pin-prick were employed. The results presented in Tables III and IV show that when the stimulus to either the normal or the abnormal area was increased, there was a corresponding increase in the mean vasoconstrictor response. Quantitative confirmation of this relationship has been obtained recently by Hovland and Riesen (1938), who recorded the vasoconstrictor responses to four intensities of electric shock, presented in random balanced order to eight normal subjects (Table II).

TABLE II.

Magnitude of vasoconstrictor responses in relation to intensity of electrical stimulation. Each value is the mean of about 12 responses in each of 8 normal subjects. The stimuli ranged by approximately equal steps from a very mild shock (1) to a moderately intense shock (4). Quoted by permission from unpublished data of C. I. Hovland and A. H. Riesen.

Strength of shock	Vasoconstrictor response (mm.)
1	11·3
2	16·5
3	19·7
4	24·4

The fifteen patients with diminished or exaggerated sensitivity to somatic stimulation have been considered in two groups. One group is composed of ten patients whose sensory disorder was due to involvement of the sensory pathway at some point below the level of the thalamus. The other group contains five patients with lesions at a thalamic or cerebral level giving rise to sensory changes. The former group contains two patients with involvement of the peripheral sensory pathway, one with dorsal root involvement, four with lesions of the spinal cord and three with lesions in the medulla or pons (fig. 2). Brief summaries of the clinical

findings of the cases relevant to the diagnosis and to the nature of the subjective sensory changes and the objective vasomotor response to various stimuli follow. A detailed summary of the experimental results is presented in Table III.

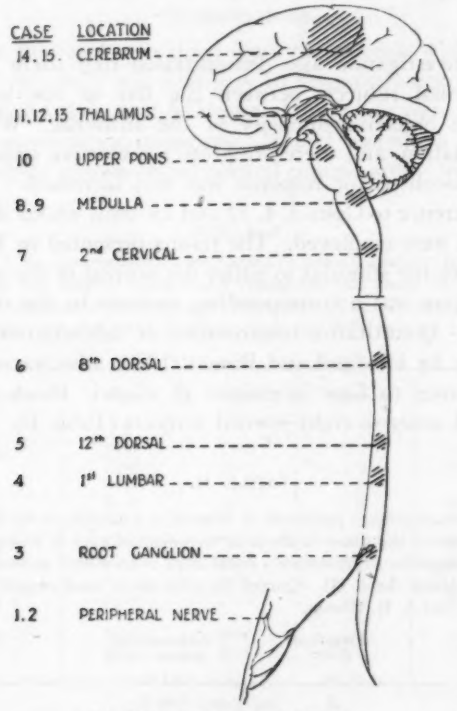

FIG. 2.

Group I.—Cases with a lesion of the sensory tract below the level of the thalamus.

Case 1.—Areas of hypo- and hyperæsthesia due to involvement of a peripheral nerve in scar tissue.

S. S., a male aged 51, was admitted under Dr. E. A. Carmichael on February 5, 1936. There was a painful scar in an amputation stump of the right thigh. There was no other abnormality of the nervous system. Sensation on the day of the experiment was as follows: Moderate pin-prick was appreciated on the hypæsthetic

area as a dull touch, unassociated with pain. With stronger stimulation pain was appreciated. At no point was there absolute anæsthesia, but the patient preferred being pricked there to the normal part. Along the posterior edge of the scar there were several minute areas of hyperalgesia where pin-prick was felt as an unpleasant

TABLE III.

Comparison of the vasoconstrictor responses in the first group of patients to stimuli on the normal and affected regions of the body. The symbols are the same as in Table I.

Case	Level of lesion	Direction of sensory change	Stimulus	Normal region	Affected region	Difference	t	P
1	Peripheral	Hyperæsthesia	Strong PP	20·1	36·0	+ 15·9	3·06	0·01
		Hypæsthesia	Strong PP	20·1	15·1	− 5·0	1·01	0·3
2a	Peripheral	Hyperæsthesia	Strong PP	7·9	17·9	+ 10·0	3·20	0·01
			Cold	7·4	16·0	+ 8·6	2·68	0·02
			Pressure	2·7	16·5	+ 13·8	6·43	0·01
2b	Dorsal 8	Analgesia	Strong PP	9·1	2·2	− 6·9	1·94	0·07
			Cold	12·3	1·2	− 11·1	2·50	0·03
3	Dorsal 5	Hyperæsthesia	Weak PP	5·0	9·8	+ 4·8	1·58	0·1
			Strong PP	7·7	15·3	+ 7·6	2·01	0·06
			Pressure	6·7	14·3	+ 7·6	1·66	0·1
			Cold	2·3	12·3	+ 10·0	3·86	0·01
4	Lumbar 1	Hyperæsthesia	Weak PP	1·0	2·2	+ 1·2	1·48	0·1
			Strong PP	2·0	9·1	+ 7·1	3·96	0·01
			Cold	2·3	12·9	+ 10·6	6·81	0·01
			Hot	1·7	4·5	+ 2·8	2·13	0·03
5	Dorsal 8	Hypæsthesia	Strong PP	8·7	1·4	− 6·3	3·39	0·01
			Cold	17·9	2·5	− 15·4	6·70	0·01
6	Dorsal 4–8	Hyperæsthesia	Strong PP	5·9	20·9	+ 15·0	3·52	0·01
			Cold	7·0	27·2	+ 20·2	4·41	0·01
7	Cervical 2	Hypæsthesia	Cold	12·8	3·3	− 9·5	3·46	0·01
8	Medulla	Hypæsthesia	Strong PP	6·8	2·6	− 4·2	2·30	0·03
			Cold	2·5	2·3	− 0·2	0·10	0·9
9	Medulla	Hypæsthesia	Strong PP	9·7	6·0	− 3·7	1·27	0·2
			Cold	7·6	4·1	− 3·5	1·59	0·1
10	Pons	Hypæsthesia	Strong PP	11·9	3·7	− 8·2	3·03	0·01
			Cold	8·6	4·9	− 3·7	1·03	0·03

shock-like sensation, unlike the ordinary sharpness of a pin. There was no radiation of the sensation. It was more unpleasant than pricking on the normal areas.

The vasomotor responses to pin-prick on the normal skin caused an average deflection of 20 mm. on the hypæsthetic area of 15 mm., and on the hyperæsthetic area of 36 mm.

Case 2.—(a) Hyperæsthesia due to involvement of peripheral nerve in scar tissue; (b) Analgesia below D.8 following subsequent chordotomy.

W. C., a male admitted under Dr. E. A. Carmichael in June, 1936, had extreme hyperæsthesia with spontaneous pain in an amputation stump of the right leg. Following a spino-thalamic section at the 8th dorsal segment there was analgesia below this level, with complete relief of his symptoms. Sensory examination before operation was as follows: In the distal third of the stump there was an area of hyperæsthesia where light touch had a rasping quality, "like sandpaper," deep pressure could not be tolerated at all, and pin-pricks caused violent withdrawals and were described as "like electric shocks." Cold produced a similar emotional over-response. Accurate descriptions of the sensations could not be obtained because of the subject's deafness and limited intellect. It was evident from comparison of the response to stimulation in other areas, however, that the hyperæsthesia was profound.

After operation there was analgesia to pin-prick, heat and cold below the 8th dorsal segment on the right. Pin-pricks were felt as dull tapping, but on extremely violent pinching with forceps a sensation of unpleasantness could be felt. Ice was described as a pleasant warmth below the level. There was a normal response to noxious stimuli elsewhere.

Before operation the vasoconstrictor responses to pin-prick and ice in the hyperæsthetic areas were over twice as great as on the normal side, while the response to pressure was six times as great. After operation the responses to pin-prick on the normal side were four times as great and to ice were ten times as great as from the analgesic area.

Case 3.—Post-herpetic hyperæsthesia.

W. H., a male, was an outpatient under Dr. J. P. Martin on February 2, 1936. In the hyperæsthetic area, which had resulted from herpes zoster of the right 5th dorsal segment, pin-prick was sharper and more painful, cold was colder, and pressure had a lower threshold and was more painful than elsewhere.

The vasoconstrictor responses to weak and strong pin-prick, pressure and cold on the affected area were increased from two to sixfold.

Case 4.—Hyperæsthesia due to a spinal cord lesion.

S. T., a male aged 27, was admitted under Dr. Grainger Stewart on January 25, 1936. There was a progressive paraplegia with flexor spasms in both legs and a sensory level at the first lumbar segment. Posterior column sensation was almost completely spared. There was increased sensitivity to pain and thermal stimulation. To pin-prick there was overaction above a raised threshold, the sensation of sharpness being lacking with moderate stimulation and a more painful component being present on stronger stimulation.

Moderate changes in temperature were normally appreciated, but there was marked overaction to extremes of temperature. Cold first felt burning hot and later felt cold, with a sharp pricking component. Heat was felt as normal below 50° C., but above this it was painfully hot and felt sharp. There was also a prolonged after-sensation. Pressure pain did not appear to be affected.

There was a significant increase in the vasoconstrictor response to graded painful

and thermal stimulation below the level. Light pin-prick on the normal and abnormal areas—below the threshold—caused closely similar responses, while strong stimulation to the abnormal area caused five times the response that was produced from the normal area. Ice caused six times the response from the abnormal area, while heat gave twice the normal response.

Case 5.—Hypæsthesia due to lesions of the spinal cord at C.3 on the right, and D.8 on the left.

W. O., a male aged 45, was admitted under Dr. E. A. Carmichael on May 20, 1936. There was marked diminution to pain and thermal sensation on the left side of the neck, with wasting of the left shoulder muscles. There was also spastic paraplegia with diminution in posterior column sensation in the legs and in lateral column sensation below the 9th thoracic segment on the right. The average vasoconstrictor response to pin-prick on the normal skin surface was six times as great, and to ice was seven times as great as on the hypalgesic areas on the right.

Case 6.—Hyperæsthesia following spinal cord injury.

H. B., a male aged 36, was admitted under the late Dr. James Collier on September 25, 1934. Following an accident the patient had spasticity and weakness of the left arm and leg, with hyperæsthesia to all forms of sensation below the 4th dorsal segment on the left, and the 8th dorsal segment on the right. It was much more marked on the right side, and was most severe distally. Details of the sensory changes at the time of the experiment were as follows: Pin-prick was sharper, more sore, and hurt more over a greater area than normal. It radiated for a few inches from the point of stimulation. Moderate cold was described as stinging, scalding, and "like ice." Heat was not appreciated as heat, but hurt and had a stinging quality in it. Light touch was described as stinging; it had an unpleasant tickle and felt stronger. Other forms of posterior column sensation were much diminished in the legs, the left being the more affected. The vasoconstrictor responses to pin-prick and to ice on the hyperalgesic area were increased nearly fourfold compared with the responses from the normal area.

Case 7.—Hypæsthesia due to spinal cord tumour.

D. B., a female admitted under Dr. C. P. Symonds, had an extra-medullary neoplasm causing damage to the spinal cord at the second cervical segment, with resulting hypæsthesia below this level. There was marked hypalgesia on the left.

The vasoconstrictor response to cold stimuli applied to the normal and abnormal areas was investigated. From the hypalgesic area it was diminished fourfold.

Case 8.—Hypæsthesia due to a lesion of the medulla.

H. H., a female aged 39, was admitted under the late Dr. S. A. K. Wilson on July 27, 1936, with the syndrome of thrombosis of the right posterior inferior cerebellar artery. There was diminution in pain sensation over the first division of the right trigeminal nerve, with diminution in pain and temperature sensation on the left side of the body which was most marked peripherally. In the left leg pin-prick was appreciated as a blunt and rather unpleasant sensation. Cold was felt as cold, but it was not at all unpleasant. It approximated more to touch

than to thermal sensation. Similarly heat was not appreciated in its normal intensity. Posterior column sensation was normal.

The vasomotor response to cold was equal on the normal and abnormal areas, but that in response to pin-prick was nearly three times as small from stimulation in the hypalgesic area as in the normal area.

Case 9.—Hypalgesia due to a medullary lesion.

A. T., a male aged 58, was admitted under Dr. F. M. R. Walshe on July 7, 1936. There was diminution to all forms of sensation over the area of distribution of the right trigeminal nerve, with involvement of pain and thermal sensation on the contralateral side of the body as a result of thrombosis of the right posterior inferior cerebellar artery. The sensory changes at the time of the experiment was as follows: Moderately firm pin-pricks were felt as vague pressure, but hard pricks caused a pain like an electric shock. The threshold for this sensation was higher than that for pain on the left side of the body. Cold was felt as a warm sensation, but lower temperatures evoked an unpleasant tingling sensation in addition. Cortical forms of sensation were normal.

On the affected side strong pin-pricks caused a vasoconstrictor response of three-quarters of the normal, and ice of about half the normal.

Case 10.—Hypalgesia due to a tumour of the pons.

L. S., a female, admitted under Dr. E. A. Carmichael on August 19, 1934, was found at operation to have a cystic glioma of the posterior part of the upper third of the pons, extending into the 4th ventricle. The clinical signs corresponded to a lesion at this level. There was relative analgesia on the left side of the face, and absolute analgesia of the right side of the body. To pin-prick there was a numb sensation with an element of unpleasantness, and ice felt like "something smooth," but was not interpreted as cold. Other forms of sensation were unimpaired.

The average vasoconstrictor response to pin-prick applied to the normal side of the body was three times as great as that resulting from stimulation of the analgesic side, while the response to cold on the normal side was nearly twice as great.

The data for the patients in this first group is summarized in Table III. It will be seen that vasoconstrictor responses closely paralleled in magnitude the subjective intensity of the sensation. In cases with diminished sensitivity the vasoconstriction elicited by stimuli applied to the affected region was smaller than normal, and in cases with exaggerated sensitivity the vasoconstriction was larger than normal. In every instance the difference between the mean values for the affected and normal regions of the body is in the direction corresponding to the sensory change, and in more than half of the twenty-six comparisons the difference is statistically reliable (i.e. there are fewer than two chances in one hundred that the observed difference is due to chance).

Case 2 provides further definite evidence that the afferent spinal pathway for the vasoconstrictor response is identical with that for conscious perception of pain. The exaggerated sensitivity to stimuli in the region of the amputation scar was accompanied by a greatly increased vasoconstrictor response. Following the cordotomy there was complete analgesia on the right side below the level of the 9th thoracic segment, and the vasoconstrictor responses likewise dropped almost to a zero value. There remained only a few small responses such as are elicited in normal subjects by light contact stimuli. It is evident that the lateral spino-thalamic tract was the afferent pathway for the hyperactive vasoconstriction response as well as for the sensory hyperæsthesia.

Group II.—Cases with a "thalamic syndrome" or with extensive cerebral destruction.

Case 11.—Hyperpathia resulting from a thalamic lesion.

F. G., a male aged 26, was admitted under Dr. Gordon Holmes on October 3, 1935. Following an accident there was a gradual onset of left hemiparesis with left sided sensory impairment and paræsthesia. There was a left hemiplegia with a continuous tremor and cogwheel rigidity. This was associated with diminution in cortical forms of sensation and very gross overaction to pain and thermal stimulation. Sensory examination at the time of the experiment revealed the following changes. Cotton-wool felt "rasping" on the left side. There was diminution to light touch on the left side of the body, measured by von Frey's hairs. Joint sense and two point discrimination were diminished on the left side, but vibration appeared to be normally appreciated. There was marked overaction to cold and pain on the left side of the body. Pin-prick was much more unpleasant, and cold was either "icy" or "scalding" on the left side. The patient winced involuntarily when stimulated on the left, but not on the right. The right side of the body was normal in all respects.

Pin-prick, ice, and pinching stimulation or symmetrical points on the two sides of the body gave equal average vasoconstrictor responses.

Case 12.—Hyperalgesia resulting from thalamic lesion.

G. J., a female aged 36, was admitted under Dr. Gordon Holmes on March 3, 1932. There was a residual hyperalgesia as a result of a vascular lesion in the right thalamus which had occurred seven years previously. When in hospital there was a tremor of the left side of the body, with left-sided paræsthesia. Heat and rough surfaces produced an "uncomfortable feeling" on the left side, that side felt "drawn up" and "tight," and there was a vague constant pain on the left. Pin-pricks and scratching were more unpleasant on the left than on the right, and even moderate heat was painful. Cortical forms of sensation were normal. At the time of the experiment much of this sensory picture had changed, but pin-prick was definitely sharper and more unpleasant above a high threshold on the left, and extremes of heat and cold were more painful on the left side of the body.

The vasoconstrictor response to heat, cold, and moderate pin-prick were equal from both sides of the body, the response to strong pin-prick was over twice as great as on the normal side, but the difference was not statistically reliable.

Case 13.—Hyperpathia, resulting from thalamic lesion.

H. M., a female aged 50, was admitted under Dr. C. P. Symonds, on May 27, 1936. Five years previously she had an embolic accident to the right thalamus, the result of mitral stenosis. She presented the classical picture of the "thalamic syndrome," with spontaneous pain, left hemiplegia, and sensory changes. The spontaneous pain was very severe, but the patient could not describe it accurately. On the left side pin-prick was diminished in acuity, but associated with a radiating and most objectionable pain. There appeared to be a raised threshold to pin-prick. Cold was not felt as cold, but as a scalding burning sensation, with a wide radiation. Pressure was accompanied by an unpleasant sickly aching sensation. Light touch gave a "nasty scraping feeling," described at various times as "tickling which is unpleasant," "scratching" and "pins and needles." Two point discrimination, stereognosis, and joint sensation were much diminished. The right side was normal.

Vasoconstrictor responses to pin-prick and cold on the two sides of the body were identical.

Case 14.—Hypæsthesia due to thrombosis of the middle cerebral artery.

T. S., a male aged 44, was admitted under Dr. E. A. Carmichael on September 9, 1935. There was a flaccid hemiplegia on the right, with "partial wasting," following apoplexy nine months previously. There was diminution in the appreciation of light touch, vibration, two point discrimination, and joint sense on the right. Pain was also impaired on that side, and discrimination of thermal difference was diminished. Pin-prick was not sharp on the right side, and did not evoke as much pain as on the normal side.

The vasoconstrictor responses to pin-prick and to ice on the two sides of the body were equal.

Case 15.—Hypæsthesia due to a parietal glioma.

E. W., a male aged 32, was admitted under Dr. D. Denny-Brown on August 1, 1936. He had a progressive flaccid hemiplegia on the left, with "parietal wasting." There was profound sensory loss to all forms of stimuli on the left side. At operation a large subcortical astrocytomatous cyst was found and aspirated where it was nearest the surface, just posterior to the fissure of Rolando.

Sensation at the time of the experiment was as follows: Light touch, vibration, joint movement and two points were appreciated with difficulty throughout the left side. There was absolute astereognosis on the left. Pin-prick was appreciated as touch only, and there was only a slight element of pain present on repeated stimulation. Moderate cold felt colder on the right, and ice did not feel like ice on the left; it evoked only a mildly cool sensation. Heat was appreciated only as warmth on the left when it was hot on the right. The difference between the feeling of pain and thermal sensations on the two sides was very marked.

The vasoconstrictor responses to mild and severe pin-prick and to ice applied to both sides of the body were identical.

Table IV summarizes the data obtained from the study of vasomotor responses in the second group of patients. The results stand in distinct contrast to those of the first group. Although the degree of sensory change was as great as that in the former group of patients, no significant alteration in the magnitude of the vasoconstriction responses was observed. This equality in the response was particularly dramatic in the three patients with the sensory overaction of the thalamic syndrome. Stimuli on the affected side of the body were reported as extremely painful and only by repeated requests could the patients be persuaded to sit quietly and continue the tests. Yet to these stimuli the vasomotor response was no greater than to the same stimuli applied to the normal side where they were endured with no signs of discomfort.

TABLE IV.

Comparison of the vasoconstrictor responses in the second group of patients to stimuli on the normal and affected regions of the body. The symbols are the same as in Tables I and III.

Case	Level of lesion	Direction of sensory change	Stimulus	Normal region	Affected region	Difference	t	P
11	Thalamus	Hyperæsthesia	Strong PP	10·4	11·9	+ 1·5	0·604	0·5
			Cold	13·4	12·4	− 1·0	0·463	0·6
			Pinch	16·7	16·3	− 0·4	0·171	0·8
12	Thalamus	Hyperæsthesia	Weak PP	2·0	2·8	+ 0·8	0·555	0·6
			Strong PP	3·2	8·7	+ 5·5	1·993	0·06
			Hot	1·9	2·2	+ 0·3	0·220	0·8
			Cold	14·4	13·3	− 1·1	0·294	0·8
13	Thalamus	Hyperæsthesia	Strong PP	4·0	3·7	− 0·3	0·186	0·8
			Cold	5·0	4·9	− 0·1	0·042	0·9
14	Cerebrum	Hypæsthesia	Strong PP	10·7	8·0	− 2·7	0·654	0·5
			Cold	14·6	16·5	+ 1·9	0·463	0·6
15	Cerebrum	Hypæsthesia	Weak PP	1·9	1·3	− 0·6	0·741	0·4
			Strong PP	31·6	34·7	+ 3·1	0·524	0·6
			Cold	2·2	2·4	+ 0·2	0·145	0·8

Cases 14 and 15 are obviously not an adequate sample of cerebral lesions and have been included in this series merely to indicate the possible effects of cerebral destruction upon the vasomotor response. The two cases were selected because of the definite and marked hypalgesia. The results obtained showed no difference between the vasoconstrictor responses to stimuli on the normal and affected side of the body, but this finding must be checked by more extensive observations. The cases are valuable, moreover, in presenting in the hypalgesia the converse of the sensory picture of

the thalamic syndrome. From the extent of the lesions and the degree of analgesia, it is probable that this sensory change was due to destruction of a part of the thalamus itself or of afferent fibres in proximity to the thalamus.

Considered as a group, the last five cases demonstrate that lesions in the cerebral hemispheres cause no significant alteration in the vasomotor response corresponding to the sensory changes, while in the first group with lesions below the thalamus the vasomotor response varies in the same direction as the subjective sensory response.

Discussion.

The peripheral efferent pathway of the vasoconstrictor response has been shown by Stürup, Bolton, Williams and Carmichael (1935) to be exclusively dependent upon the sympathetic nerves. The diminution in digital volume following sensory stimulation was abolished by section of the sympathetic innervation of the digit and remained unaffected by destruction of the dorsal and ventral root fibres supplying the digit when the sympathetic nerves were intact, as is the case in a cauda equina lesion. Destruction of peripheral sensory nerves rendered it impossible to elicit vasoconstrictor responses from the anæsthetic area. Doupe, Robertson and Carmichael (1937) showed that destruction of the dorsal root fibres in the cauda equina produced a similar result, thus demonstrating that the sympathetic nervous system in man depends for its afferent pathway on the somatic sensory nerve fibres.

Although the extramedullary pathway of the vasomotor arc has been established, its intramedullary course is not accurately known. Ranson and Billingsley (1916, b) have suggested, on the basis of experimental lesions in cats, that the ascending pressor vasomotor pathway in the spinal cord lies in the tract of Lissauer at the apex of the posterior horn. Evidence from the present study, however, demonstrates that the afferent pathway of the vasoconstrictor response is identical with the sensory pathway. Affections of the peripheral sensory nerves, of the dorsal root ganglia, and of the intraspinal tracts which cause increased or decreased sensitivity to somatic stimuli also cause a corresponding increase or decrease in the resulting vasomotor responses.

In the first group of cases, those with lesions of the sensory pathway below the thalamus, the correlation between the degree of sensory disturbance and the alteration in the vasoconstrictor response was striking in every subject. It is true that lesions of the central nervous system in man, however discrete, cannot have the same localizing significance as experimental lesions in animals. Nevertheless, such a correlation makes it extremely

likely that the sensory and vasomotor afferent pathways are identical. Furthermore, in both the normal and abnormal subjects, the vasomotor responses varied with the intensity and the subjective appreciation of the stimulus. Were the intramedullary afferent pathway of vasoconstrictor response different from that for pain, it is extremely unlikely that such a correlation would have been found in all these circumstances. Experimental confirmation of this conclusion is given by Case 2, in which an abnormally great vasoconstrictor response was virtually abolished by section of the spino-thalamic tract.

The lack of correspondence, on the other hand, between subjective sensory intensity and vasomotor response in the second group of subjects—patients with thalamic and cerebral lesions—makes it evident that the two pathways are not identical in the cerebrum. In these five cases there was a very profound alteration, both increase and decrease, in sensations evoked by stimuli which were adequate for the vasoconstrictor response, but there was no comparable change in the vasomotor response. Two reasons are possible for this—a divergence of the afferent sensory and vasomotor pathways, or a termination of the vasomotor afferent fibres below the level of the lesions. It is unlikely that the lesions in these five cases would all have spared the afferent vasomotor fibres, with such definite involvement of the sensory pathways. The more probable explanation is therefore that the central arc of the vasoconstrictor response is complete below the level of the cerebrum. Further evidence that the vasomotor arc does not ascend to the cerebrum has been given by Stürup, Bolton, Williams and Carmichael (1935) who showed that diverse lesions of the cerebral hemispheres resulting in hemiplegia caused no change in the vasoconstrictor responses to sensory stimuli. On the other hand, Schwartz (1937) has reported that the removal of the area frontalis agranularis (Area 6 of Brodmann) of the cat's cortex abolishes the galvanic skin response in the contralateral limbs to sensory stimuli such as noise, pinch and pain. Whether this result, which stands in clear contrast to the absence of effect of cerebral lesions in man, will be found due to a difference in the subjects used, in the response studied, or in the cerebral areas involved, must be determined by further observations.

From the present experimental knowledge of the central control of sympathetic activity and from unpublished observations which are being accumulated on the effect of lesions in man it would appear that the vasomotor arc involves the hypothalamus. Since there was no overaction of the vasomotor response corresponding to the sensory overaction in the patients with the thalamic syndrome, it is plausible to postulate that the hypothalamus receives its sensory input by way of collaterals leaving the ascending sensory tract before it terminates in the thalamus, rather than by

collaterals of the thalamo-cortical projection fibres. This view receives support from the experiments of Bard (1929) in which it was found that removal of the cerebral hemispheres and most of the dorsal thalamus in cats did not abolish the sympathetic responses characteristic of "sham rage."

The absence of cerebral influence upon the vasomotor response to somatic stimuli does not necessarily imply the absence of any influence upon other forms of vasomotor or sympathetic activity. It is clear that vasoconstrictor responses can be instituted by word association, mental effort, fear and apprehension, and other processes which undoubtedly depend on cortical functioning. Many experimenters, whose investigations have recently been reviewed by Kennard (1937), have found that stimulation of the pre-Rolandic areas gives rise to vasomotor and other sympathetic changes. Moreover, the extirpation of these cerebral areas in animals, or their involvement in pathological lesions in man, may be followed by vasomotor changes in the contralateral limbs as evidenced by an increased or a decreased skin temperature relative to the normal side. The relation of this form of cerebral influence upon vasomotor activity to the absence of such influence upon vasomotor responses to sensory stimuli awaits further experimental study.

The existence of a vasomotor centre in the medulla has long been recognized. Electrical stimulation of the caudal end of the floor of the 4th ventricle in cats has been shown to cause at one point a rise in blood-pressure, and at another point a fall in blood-pressure (Ranson and Billingsley, 1916, a). That the medullary centre is not adequate for mediation of vasoconstrictor responses to sensory stimuli in man, however, is clearly shown by the results of Cases 8, 9 and 10. Lesions of the sensory pathway above the level of the medullary centre caused marked alteration of the magnitude of the vasoconstrictor response. It is likely that the centre in the medulla is concerned with vasomotor regulation in response to vagus and associated afferent impulses and not to somatic stimulation.

If the vasomotor response to sensory stimulation is not affected by thalamic and cerebral involvement of the sensory pathways, it should follow that hysterical anæsthesia and hypnotically induced anæsthesia should be without effect on such responses. Levine (1930) found no change in the galvanic skin response to stimuli in the anæsthetic region of hysterical and hypnotized individuals, but his data was not complete enough for statistical comparison of the size of the responses. Sears (1932), in a more extensive controlled study, measured certain skeletal and sympathetic responses in individuals rendered anæsthetic in one limb by

hypnotic suggestion. Although the flinching response and the change in respiratory movements caused by pain stimuli were eliminated by hypnotic anæsthesia, there was no significant alteration in the size of the galvanic skin response or the sphygmographic record of the pulse. More specific study of vasoconstrictor responses under hypnotic anæsthesia will be published in the near future.

The results of the present study have bearings on the theory of emotion. According to the well known James-Lange conception, the experienced emotion is the perception of the muscular and visceral changes which occur in response to the emotional stimulus. The quality and the intensity of the emotion will vary with the nature and magnitude of the bodily changes. A correlation between the size of the sympathetic response and the reported intensity of pain was found in the normal subjects and in the patients of Group 1 whose lesions involved the sensory pathway below the level of the thalamus. This correlation does not imply an *essential* relationship, however, for in Cases 11 to 15, the exaggerated or diminished sensory experience was not accompanied by any corresponding alteration in the magnitude of the vasomotor reaction. This result supplements the already large body of experimental data adverse to the James-Lange theory (Cannon, 1927).

Prominent in recent discussions of the neurological mechanism of emotion is the conception that thalamic function determines the nature of emotion and emotional response subject to inhibitory control by the cortex. Two observations provide the foundation of this conception: (1) that decorticate animals respond to painful or emotional stimuli by an exaggerated reaction involving a generalized sympathetic discharge (Bard, 1929); and (2) that in certain patients exhibiting emotional overreaction to painful stimuli (thalamic syndrome), it has been found that the pathological lesion sometimes involves the region of the thalamus, and presumably interrupts a cortico-thalamic inhibitory pathway (Head, 1920). The first fact deals only with observed behaviour response; the second, only with the reported sensory experience. If the two observations refer to the same process, however, it should be possible to demonstrate an increased sympathetic response in patients with the emotional overreaction of the thalamic syndrome. In the three patients of this type studied by us (Cases 11, 12, 13), there was clear evidence to the contrary. No exaggeration of vasomotor reactions to stimuli which evoked intense sensory unpleasantness was observed. It is evident that the exaggerated "emotion" of decorticate animals and of patients with thalamic syndrome is not the same thing. Other evidence of a clinical nature has cast serious doubt on the explanation of the thalamic syndrome as a release from cortical inhibition (Wilson, 1927; Davison and Schick, 1936).

SUMMARY.

The central neural mechanism of the vasoconstrictor response to sensory stimuli has been investigated by plethysmographic recording of vasomotor changes in five normal subjects and fifteen patients with discrete lesions of the nervous system involving the sensory pathway.

It has been found that in normal subjects the vasoconstrictor responses to equal stimuli on symmetrical skin areas are equal, and that they vary directly with the intensity of the stimulus.

In ten subjects with lesions of the sensory pathway below the level of the thalamus the vasomotor response varied directly with the change in the subjective appreciation of the stimuli, while in five subjects with lesions of the sensory tracts in the thalamus or cerebrum, there was no effect on magnitude of the vasoconstrictor response.

The evidence presented suggests that in man the ascending pathway for the vasomotor response to somatic stimulation is the spino-thalamic tract, and that the vasomotor reflex arc is complete in the brain-stem below the level of the sensory thalamus.

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VASOMOTOR CONTROL OF CEREBRAL VESSELS.

BY HENRY S. FORBES AND STANLEY S. COBB.

(*Boston*).

VASOMOTOR regulation in the brain is different from that in other organs. In the past, investigators have laid great emphasis on the passive behaviour of vessels in the brain. Bayliss (1895) wrote:—

> ". . . . there is no adequate evidence that the cerebral vessels have any vasomotor control ; the importance of the brain is such that its circulation is regulated by the whole of the rest of the body, which is caused to accommodate itself, by constrictor or dilator nerves, to the needs of the brain. (Bayliss, Hill and Gulland, 1895.)

The latter part of this statement, certainly, is confirmed by recent careful observations—those, for example, of Rein (1931) and of Bouckaert and Heymans (1933, 1935) who show in detail how the carotid sinus and other reflexes cause a redistribution of blood in favour of the brain. In man satisfactory proof of the existence of vasomotor control of cerebral vessels is still lacking (Carmichael, Doupe and Williams, 1938).

During the past few years, however, workers in different laboratories, using different experimental methods, have obtained convincing evidence that in animals cerebral vasoconstrictor nerves do exist, but that they exert slight influence on arterial calibre (Forbes and Wolff, 1928 ; Forbes, Finley and Nason, 1933) or on cerebral blood flow (Schmidt, 1934-35, 1935-36 ; Noyons, Westenrijk and Jongbloed, 1936 ; Norcross, in press ; Bouckaert and Jourdan, 1936, a) compared with the effect of constrictor nerves in other organs. Many other workers are in agreement with these findings (Finesigner and Putnam, 1933 ; Franke and Seager, 1932 ; Aske-Upmark, 1935 ; Thomas, 1936 ; Tinel and Ungar, 1936 ; Fog, personal communication). A vasodilator mechanism has also been described (Cobb and Finesinger, 1932 ; Chorobski and Penfield, 1932 ; Forbes, Nason, Cobb and Wortman, 1937). Furthermore, improved histological methods have demonstrated beyond question the presence of nerve fibres—myelinated and non-myelinated—on the cerebral vessels and meninges both in animals and in man (McNaughton, 1938).

To get a clear idea of the part played by the vasomotor apparatus, it may be well to review the many factors which regulate the blood flow

through the brain. Within the past three years information has been obtained which for the first time permits a reasonably accurate summary of these factors. They may be divided into two main groups—indirect and direct, or extracerebral and cerebral (Table I).

TABLE I.

FACTORS REGULATING BLOOD FLOW IN BRAIN.

Extracerebral
  Systemic Arterial Pressure
Cerebral
  Active Changes in Arterial Calibre due to:—
    A. Direct trauma.
    B. Chemical changes in arterial blood—CO_2 ; drugs.
    C. Asphyxia of tissues from slow blood flow.
    D. Local neuron activity—local increase in flow.
    E. Vasoconstrictor nerves—sympathetic.
    F. Vasodilator nerves—parasympathetic.
  Passive Changes in Arterial Calibre.

EXTRACEREBRAL FACTORS.

The Systemic Arterial Pressure.

This factor appears to dominate all others. The arterial pressure, in turn, depends on complex reflexes from the cardiovascular centres of the central nervous system, the carotid sinuses and other reflex mechanisms. These reflexes, therefore, play a vital part in controlling the supply of blood to the brain (Bouckaert and Heymans, 1933 ; Weiss and Baker, 1933). Other factors contribute to this end: the resistance of arterioles throughout the body, the amount of venous blood returned to the heart and the state of the heart itself.

CEREBRAL FACTORS.

Active Changes in Calibre of Cerebral Arteries.[1]

Such changes in calibre, due to changes in tonus of the arterial walls, may overcome moderate or gradual fluctuations in arterial pressure (Fog, 1934 : Forbes, Nason and Wortman, 1937 ; Fog, 1937). Thus, when active changes occur, we usually find arterial constriction following a rise in

[1] By the term "active changes in calibre" we mean changes due to alterations in the state of contraction and relaxation of the muscle fibres of the arterial walls (tonus). The fact that the arteries do not behave like inert collapsible tubes (varying in size directly with the internal pressure) indicates that active work is performed by their walls.

blood-pressure and dilatation following a fall. An explanation for this inverse relationship between arterial calibre and intravascular pressure is suggested below in paragraph (*c*).

Active changes in calibre result from the following conditions:—

(*a*) Direct trauma to vessel walls.

(*b*) Changes in chemical composition of the arterial blood. Variations in tension of arterial CO_2 are of first importance, for CO_2 strongly dilates all cerebral vessels (Wolff and Lennox, 1930). Many drugs (nitrites, alcohol) and inhaled gases (CO, H_2S) act in a similar fashion.

(*c*) Asphyxia of the tissues due to slow blood flow (termed by Van Slyke "stagnant anoxia"). This condition in the brain may result from general or local causes: low blood-pressure, high intracranial pressure or occlusion of vessels supplying the brain. In all of these states we have seen the cerebral arteries dilate (Forbes, Nason and Wortman, 1937). Partial compensation for the slowing of blood flow is thus established. The dilatation is probably due to a chemical (asphyxial) effect on the arterial walls,[1] not to a nerve reflex, for it is unaffected by cocaine or by atropine applied locally to the vessels (Forbes, Nason and Wortman, 1937). When the blood-pressure rises again, the relaxed walls may dilate still further for a few seconds, but then (while the pressure is still rising) constriction steadily takes place as the asphyxial condition is relieved by the more rapid flow.

(*d*) Regional activity of the brain. There is evidence that active areas of grey matter have a local vasodilatation (Cobb and Talbott, 1937; Feitelberg and Lampl, 1934-35; Gerard and Serota, 1936). This may be due to a local increase in CO_2 or other products of active cellular metabolism.

(*e*) Activity of cerebral vasoconstrictor nerves (sympathetic).

(*f*) Activity of cerebral vasodilator nerves (parasympathetic).

These last two conditions have less effect on cerebral blood flow than the chemical conditions mentioned under (*b*), (*c*) and (*d*).

Passive Changes in Calibre of Cerebral Arteries.[2]

Distension or slight narrowing may occur during abrupt fluctuations of blood-pressure. Such changes in calibre are obviously due to mechanical

[1] A possible explanation for this effect may be the following: the muscle fibres within the arterial walls produce CO_2 as a result of their own metabolism. The CO_2 diffuses into the lumen and is carried off by the blood. When the rate of blood flow is diminished the tension of CO_2 increases in the muscular coats, owing to delayed elimination through the lumen. The increased tension of the gas relaxes the muscle fibres and allows the intravascular pressure to dilate the artery.

[2] These changes, although ocurring within the brain, are really of extracranial origin, for they depend on changes in arterial pressure.

causes. These passive changes in calibre are transient, however, and slight in extent, unless the vessel walls are in a relaxed state. In that case, a rise in intravascular pressure may cause extreme dilatation.

The main object of this paper is to discuss the neural vasomotor mechanism of the brain and to present in some detail the results of recent experimental work. Various methods have been used, both indirect and direct. Each method has its advantages and its drawbacks. These have been reviewed critically by Bouckaert and Jourdan (1936, a). The recent indirect evidence will be given first.

Vasoconstriction.

Schmidt (1934-35, 1935-36) and Schmidt and Pierson (1934), using a thermo-electric method, obtained evidence of retarded flow on stimulation of the cervical sympathetic nerve. This effect was noticeable chiefly in the parietal cortex, less in the hypothalamus and still less (or doubtful) in the medulla. The change in flow appeared to be independent of changes in blood-pressure, but the extracranial circulation was not excluded in these experiments.

Noyons, Westenrijk and Jongbloed measured changes in blood flow with a Gibbs' thermo-electric recorder imbedded in the cortex of dogs, cats and rabbits (the latter non-anæsthetized). The results confirm those of Schmidt: stimulation of the cervical sympathetic trunk caused a slight retardation of the cerebral blood flow coincident with a strong constriction of the arteries of the ear and a small rise in blood-pressure.

Still more recently Norcross has also completed a careful investigation using similar methods. His results confirm those of Noyons and of Schmidt.

Bouckaert and Jourdan (1936, a), using three different methods, eliminated completely the extracranial circulation by a radical operation, and perfused the isolated head. On stimulation of the cervical sympathetic nerve they obtained evidence of vascular constriction and a reduced flow through the brain. Many investigators using perfusion experiments have obtained similar but less convincing evidence. Their work is summarized by Bouckaert and Jourdan.

In our own laboratory, by the use of a cranial window and microscope, we have observed and recorded the changing diameters of vessels in the pia-arachnoid over the parietal cortex. For this work we have used mostly cats, a few dogs and several monkeys. Our findings, some of them not yet published, may be summarized as follows:—

In a large series of experiments, on more than 300 animals, stimulation of the cervical sympathetic nerve has resulted consistently in constriction

of arteries in the pia. We have found that the sympathetic fibres responsible for the reaction pass through the middle ear in close association with the caroticotympanic nerves. The latter serve as pathways for the sympathetic fibres which dilate the pupils (Kuntz, 1934). Sympathetic nerve fibres via the stellate ganglion and vertebral nerves exercise no influence, so far as we could determine, on pial arteries of the parietal region. The time relations and magnitude of the response can be seen in the graphic records.

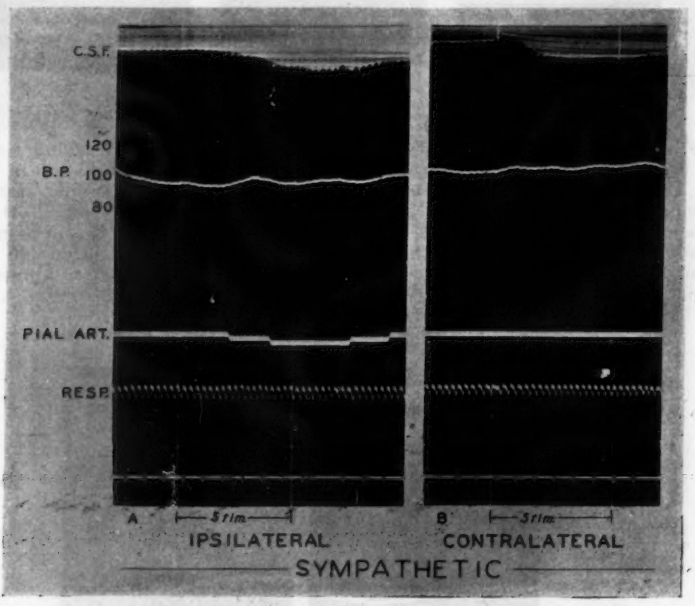


FIG. 1.—Stimulation of the ipsilateral and the contralateral sympathetic nerves (coil distance 12 cm. in "A" and "B"). A. Ipsilateral sympathetic: The pial artery, 143 μ in diameter, constricted 5 per cent. B. Contralateral sympathetic: The same pial artery did not change. The blood-pressure changed little during either stimulation and the cerebrospinal fluid pressure fell each time in the same manner. In this figure and in figs. 2, 3, 5, 8 and 9 the signal line (when shown) is at the bottom, and two vertical lines indicate the period of stimulation. The time marker records five second intervals. The stimulation was made with a faradic current (Harvard inductorium).

The chief characteristics of this arterial constriction are as follows:—

(1) It is strictly ipsilateral, that is, the vasoconstriction occurs only on the same side of the head as the nerve stimulated. No exceptions to this rule have been observed (fig. 1).

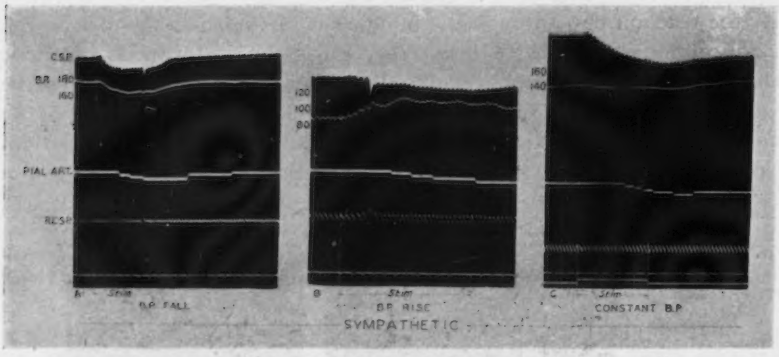


FIG. 2.—Stimulation of the cervical sympathetic nerve, showing a falling, a rising and a constant blood-pressure during the stimulation (coil distance 13 cm. in "A" and 12 cm. in "B" and "C"). A. The blood-pressure (178 mm. Hg.) fell 14 mm.; and the pial artery, 169 μ in diameter, constricted 8 per cent. B. The blood-pressure (88 mm. Hg.) rose 28 mm.; and the pial artery, 117 μ in diameter, constricted 11 per cent. C. The blood-pressure remained constant (at 140 mm.) throughout the stimulation; and the pial artery, 114 μ in diameter, constricted 14 per cent. The cerebrospinal fluid pressure fell with each stimulation.

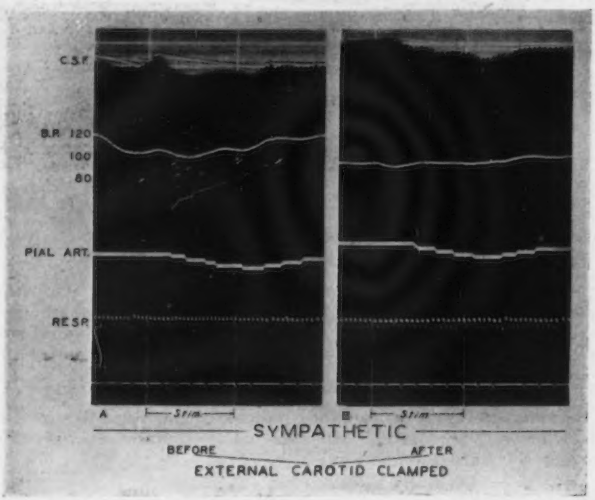
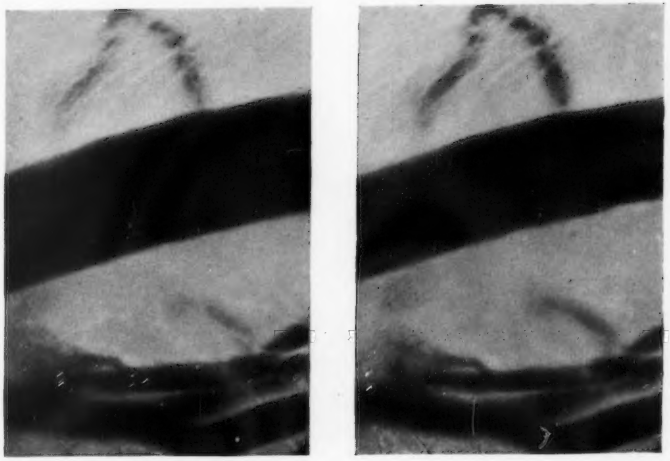


FIG. 3.—Stimulation of the cervical sympathetic nerve before and after the ipsilateral external carotid artery was clamped (coil distance 13 cm. and angle 15° in both "A" and "B"). A. The pial artery, 169 μ in diameter, constricted 10 per cent. B. The pial artery, 186 μ in diameter, constricted 7 per cent. The cerebrospinal fluid pressure fell with each stimulation, and the blood-pressure changed little during either stimulation.

PLATE IX.

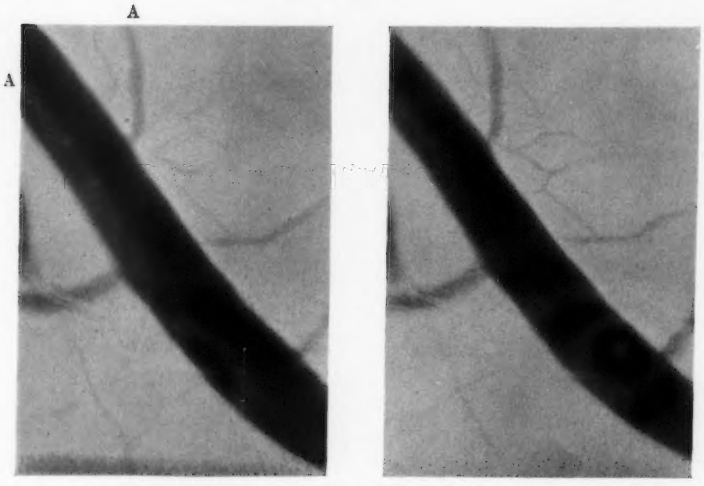


(*a*) (*b*)

FIG. 4.

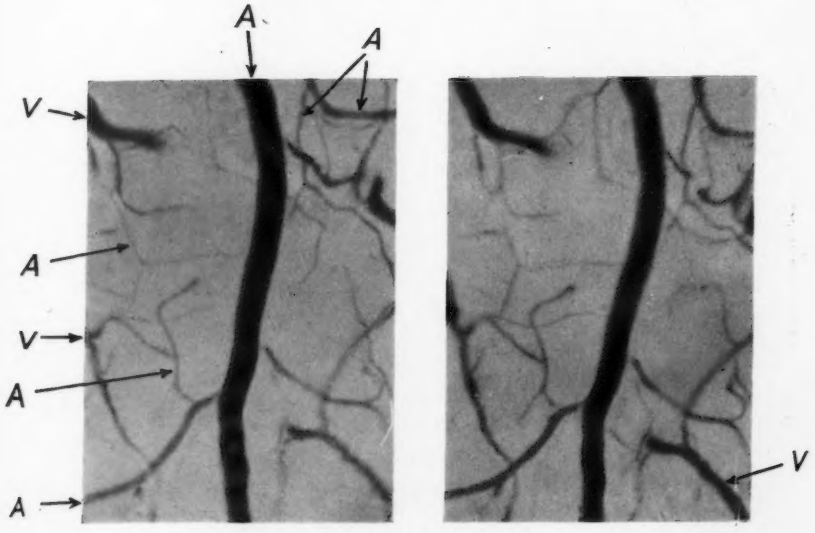
To illustrate article by Henry S. Forbes and Stanley S. Cobb.

PLATE X.



(*a*) (*b*)

FIG. 6, a.

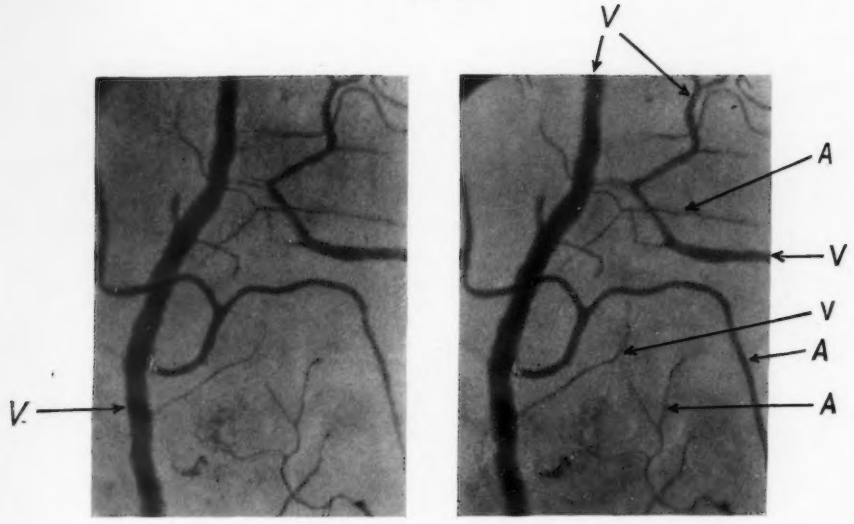


(*a*) (*b*)

FIG. 6, b.

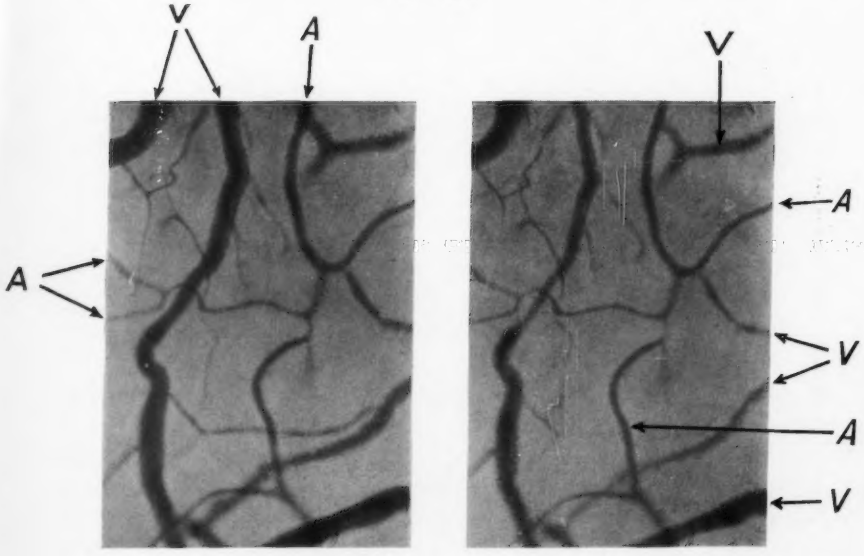
To illustrate article by Henry S. Forbes and Stanley S. Cobb.

PLATE XI.



(a) (b)

FIG. 6, c.



(a) (b)

FIG. 6, d.

To illustrate article by Henry S. Forbes and Stanley S. Cobb.

(2) It appears to be independent of changes in systemic arterial pressure, since it takes place when the latter is rising, is falling, or is constant (fig. 2).

(3) It occurs even when the greater part of the extracranial circulation is eliminated by clamping one or both external carotid arteries (fig. 3).

(4) It occurs in the completely isolated head, perfused through the carotid arteries of another animal. This fact as well as its unilateral character show definitely that humoral substances are not responsible for the reaction (Pool, Forbes and Nason, 1934, a) (fig. 4).

(5) It is abolished by the previous application of cocaine, novocain, or ergotamine locally to the pial arteries under observation (fig. 5). Such

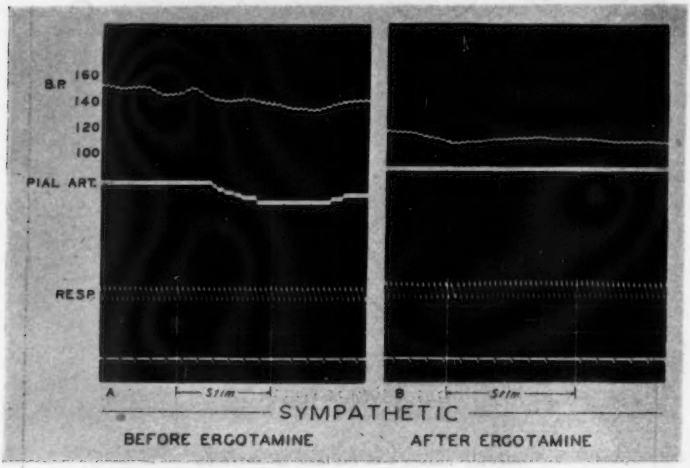


FIG. 5.—Stimulation of the cervical sympathetic nerve before and after ergotamine tartrate (coil distance 13 cm. in "A" and "B"). A. The pial artery, 182 μ in diameter, constricted 11 per cent. B. 1 c.c. of a 1:2,000 solution of ergotamine tartrate ("Gynergen") was applied locally beneath the cranial window six minutes before this stimulation. The pial artery did not change.

procedures would be expected to inactivate nerve elements in the walls of these vessels. The action of ergotamine confirms the fact that the nerves involved are of sympathetic origin.

(6) It has been observed consistently only with arteries larger than 50μ in diameter (fig. 6). With the smaller arterioles and capillaries no consistent change in calibre has been seen. It is interesting that Penfield (personal communication) found histological evidence of nerve fibres only on arteries above this size.

(7) The amount of constriction is small—an average narrowing of only 8 per cent. has been observed.

(8) Compared with the vasoconstriction observed in other organs, that in the brain is slight. When the cervical sympathetic nerve is stimulated, arteries in the skin constrict ten times as much as those in the pia (fig. 7)

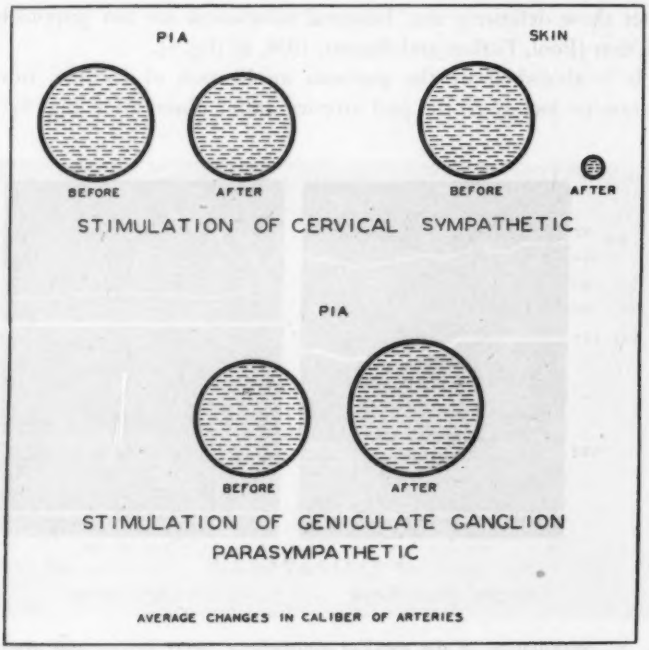


FIG. 7.—The circles are drawn to show the average changes in the cross-sectional area of arteries after stimulation of the cervical sympathetic nerve and after stimulation of the geniculate ganglion. The averages were obtained as follows: Stimulation of cervical sympathetic—*Arteries of pia*: 100 stimulations (30 cats and 1 monkey). Average diameter before stimulation was 169 μ Average constriction was 8 per cent. *Arteries of skin*: 10 stimulations (2 cats and 1 monkey). Average diameter before stimulation was 182 μ. Average constriction was 80 per cent. Stimulation of geniculate ganglion (parasympathetic)—*Arteries of pia*: 115 stimulations (20 cats). Average diameter before stimulation was 195 μ Average dilatation was 16 per cent.

and in the dura the arteries constrict almost eight times as much (Pool, Forbes and Nason, 1934, b).

This accumulated evidence seems fairly complete. Some of our observations, however, are at variance with the usual picture of vasomotor

innervation, and no satisfactory explanation has yet been found for these atypical reactions.[1]

When the cervical sympathetic trunk is cut, and the superior cervical ganglion removed, we have seen no subsequent dilatation of the pial arteries that we were watching under the window.

When cocaine is injected intravenously there is no evidence of increased sensitivity of the sympathetic vasoconstrictor reaction in the pia, such as Rosenblueth and Cannon have found elsewhere.

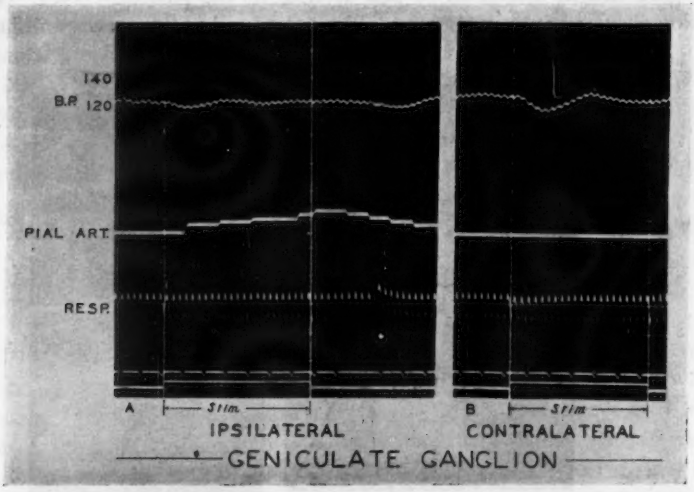


FIG. 8.—Stimulation of the ipsilateral and the contralateral geniculate ganglia (coil distance 13 cm. in "A" and "B"). A. Ipsilateral geniculate ganglion. The pial artery, 162 μ in diameter, dilated 12 per cent. The blood-pressure (124 mm. Hg.) remained nearly constant throughout the stimulation. B. Contralateral geniculate ganglion. The pial artery, 159 μ in diameter, did not change in calibre. The blood-pressure (128 mm. Hg.) fell 12 mm.

No increased sensitivity of the arteries follows denervation. When the superior cervical and stellate ganglia are removed and suitable time is allowed for degeneration of the nerve endings, adrenalin applied locally to the pial arteries causes no greater constriction than it does in the normal animal (White and Forbes, unpublished).

The venules in the pia constrict as much as, or more than, the small

[1] In recent experiments we have found that atropine solution (1 or 0·5 per cent.) applied locally to the vessels abolished the constriction due to sympathetic nerve stimulation.

arteries when adrenalin is applied locally. Also, the venules sometimes constrict in response to stimulation of the cervical sympathetic nerve (fig. 6, d).

Vasodilatation.

Evidence of a vasodilator innervation was first obtained in a joint experiment with Penfield conducted in our laboratory (Cobb and Finesinger, 1932 ; Chorobski and Penfield, 1932). On a sympathectomized monkey it was shown that stimulation of the facial nerve near the medulla oblongata caused dilatation of pial arteries in the parietal cortex. This reaction occurred only on the same side of the head as the nerve stimulated.

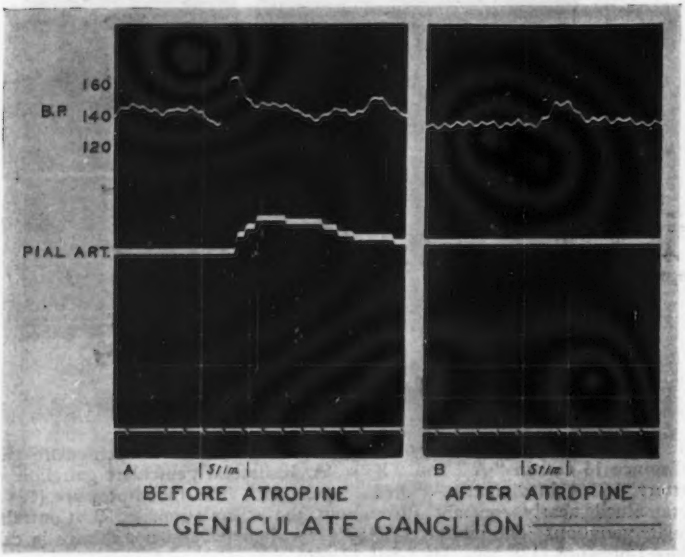


FIG. 9.—Stimulation of the geniculate ganglion before and after local atropine (coil distance 13 cm. and angle 20° in "A" and "B"). A. The pial artery, 182 μ in diameter, dilated 14 per cent. B. 1 c.c. of a 0·5 per cent. solution of atropine sulphate was applied locally beneath the cranial window eighteen minutes before this stimulation. The pial artery, 188 μ in diameter, did not change. The blood-pressure rose promptly during each stimulation.

The further evidence may be summarized as follows:—

Anatomical and histological work by Chorobski and Penfield shows that nerve fibres pass from the facial nerve through the geniculate ganglion and the great superficial petrosal nerve to the carotid nerve ascending the internal carotid artery.

Physiological experiment shows that:—

(1) Stimulation of the facial nerve at the geniculate ganglion causes prompt dilatation of arteries in the pia-mater of the parietal region (Forbes, Nason, Cobb and Wortman, 1937) (fig. 7). In these experiments the facial nerve was cut between the point of stimulation and the medulla.

(2) This reaction is always ipsilateral in character[1] (fig. 8).

(3) Vasodilatation occurs when the blood-pressure is normal at the beginning and remains nearly constant throughout the period of stimulation. This is important, because it has been found that if the systemic arterial pressure falls below a certain critical level the pial arteries always dilate as a consequence of the retarded blood flow.

(4) Local applications of cocaine and of atropine abolish this reaction, though they have no effect on the dilatation due to low blood-pressure. This action of atropine is especially significant since it indicates that parasympathetic nerve elements are involved (fig. 9). Ergotamine (locally) does not affect the reaction.

These observations have yet to be confirmed by other workers using different experimental methods.

Comment.

In regard to the functional importance of the cerebral vasomotor mechanism the evidence at hand warrants only a few suggestions. Since it is more effective in some parts of the brain than in others it may aid in diverting the blood from one region to another; it may help arteries to regain their normal calibre, as after extreme dilatation, and it may limit undesirable fluctuations and thus aid in maintaining a steady rate of flow through the brain. But there is no evidence from experimental work to show that it can cause the arteries to shut down sufficiently to bring about ischæmia.

Summary.

The former confusion regarding regulation of blood flow within the brain and its meninges has been clarified by recent experiments carried on independently in different laboratories. To-day there seems to be substantial agreement on several points; that an intracerebral regulation does exist; that in this regulation chemical agents (especially CO_2) play a major

[1] It was thought at first that the vagal centre in the medulla was somehow connected with the facial nerve pathway for dilator impulses to the pial arteries. Later it was found that the bilateral dilatation of these vessels, which follows vagus stimulation, was caused by the fall in blood-pressure, and was distinct from the reaction caused by stimulation of the facial nerve.

part; that cerebral vasoconstrictor nerves are present but that they are only about one-tenth as effective in the pia as the vasoconstrictor nerves are in the skin; that vasoconstrictor nerves are distributed unequally to different parts of the brain. Evidence has been obtained also for the existence of cerebral vasodilator nerves.

With so many regulatory mechanisms one might expect frequent changes in vessel calibre and in blood-flow, even under resting conditions. Such changes do not occur normally. The capillaries, at least in the pia, appear to be always open, the arterioles do not change in size appreciably and the flow is remarkable for its steadiness.

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LEGENDS FOR PLATES IX, X, XI.

FIG. 4.—Photomicrographs of pial vessels in the isolated head taken before and after stimulation of the ipsilateral sympathetic nerve in the isolated head (coil distance 12 cm.). The pial artery, 322 μ in diameter, constricted 12 per cent. In this figure and in fig. 6 the photomicrographs were taken with a Leica camera; Persenso film, objective $\times 10$, ocular $\times 10$. "A" indicates arteries or arterioles, and "V" indicates veins or venules. (*a*) Before stimulation. (*b*) After stimulation.

FIG. 6.—Photomicrographs of pial vessels taken before and after stimulation of the ipsilateral sympathetic nerve in four different experiments (coil distance 13 cm. in "A," 11 cm. in "B," 12 cm. in "C" and "D"). A. The artery, 188 μ in diameter, shows definite constriction. (*a*) Before, and (*b*) after stimulation. B. The largest artery in the field, 62 μ in diameter, shows a definite constriction. Some of the veins and small arterioles constricted slightly, others appear to be larger. The photomicrograph taken after the stimulation was not properly focused and the photographic field was shifted slightly. Therefore, it is difficult to be sure about the smallest vessels. (*a*) Before, and (*b*) after stimulation. C. The venules and arterioles changed little, if at all, in this experiment. However, in the same experiment, larger arteries constricted in the characteristic manner after stimulation of the sympathetic nerve. (*a*) Before, and (*b*) after stimulation. D. The veins and venules show a marked constriction. The small arterioles also constricted in this experiment. (*a*) Before, and (*b*) after stimulation.

Notices of Recent Publications.

Ueber die Untersuchung der musikalischen Funktionen bei Patienten mit Gehirnleiden, besonders bei Patienten mit Aphasie. By H. J. Ustvedt. Helsingfors. 1937. *Act. Med. Scand. Supplement,* 86. Mercators Tryckeri. Pp. 737. (With French and English summaries.)

The function of language occupies a special rank of obscurity in the provinces of both normal and morbid physiology. Light shed from any angle, however oblique, is especially welcome if it can in any way illumine certain aspects of aphasia. The role of the musical faculty in speech disorders, though hitherto somewhat neglected, possibly for reasons of technical difficulty, suggests a possible line of assault upon the major problem. This present monograph of Ustvedt's is therefore twice welcome: first because it attacks an obscure but potentially important subject and secondly because it successfully emerges as a detailed yet shrewdly reasoned treatise. Previous contributions are singularly speculative and unhelpful, being largely concerned with isolated cases, inadequately studied—especially with regard to the general psychological state. (Exceptions must be made in the case of Henschen and Feuchtwanger.) It is interesting to find that impaired musical function seems almost always to be associated with other psycho-somatic disorders—especially of speech; pure musical defects do not appear to have been recorded as isolated phenomena. The author offers a number of suggestions for future research and demands a more systematic routine examination of musical function in normal as well as aphasic subjects. He points out that music must not be regarded as a mere appenage of speech, but rather as a totally distinct faculty which, though perhaps possessing a common origin, has early parted ways, losing almost all traces of symbolic purpose. A close and interesting discussion of the psychological nature of musicality is followed by a clinical section. The author's material comprises nineteen cases, mainly of left-sided cerebral lesions. The case-records are very carefully analysed with sympathetic yet critical reference to the modern conceptions of aphasia due to van Woerkom, Goldstein, and others. A lowering of the general emotional level was demonstrable in the musical faculty also. Musical defects do not necessarily accompany an abasement of the general intellectual capacity, and severe aphasia may occur with a relatively unimpaired musical function. From his close scrutiny of the data, Ustvedt has to conclude that our knowledge is still far too superficial to permit any generalizations as to the pathology of musical function. Questions of localization must also remain in the air, although it is interesting to note that in every patient with symptomatic defects of musical function there has been a lesion in the left hemisphere. One must bear in mind, however, that such material is of a selected character.

Ustvedt's monograph is undoubtedly the most important contribution to this aspect of the problem of aphasia.

Chemistry of the Brain. By IRVINE H. PAGE. London: Ballière, Tindall and Cox. Pp. 444. Price 34s.

The chemical changes occurring in the brain in disease offers a new field of research which has but recently received any serious consideration. The author in this extremely well-written and fully documented book has attempted to collect all the recent work on this subject, together with a detailed account of the chemistry of those substances that occur normally in the brain.

These various chemical substances have been discussed in a series of chapters, the latter part of each chapter containing the work that has been undertaken in various diseases in relation to such substances.

Physical chemistry and oxidation processes have been treated in a similar manner. One rather noticeable feature is the relative absence of discussion on changes found in organic nervous disease, but this is explained by the surprising lack of reliable original work.

A large number of observations have been made in mental disorders and these are critically reviewed by the author. For the most part he has very ably discussed all the material at his disposal.

One short chapter on the Brain and Thought, however, is hardly related to brain chemistry.

This work is a comprehensive survey and will be of great value to those who are interested in this subject.

Occupational Treatment of Mental Illness. By J. IVISON RUSSELL. London: Ballière, Tindall and Cox. 1938. Pp. 231. Price 6s.

This eminently practical handbook will be welcomed by all those who may be responsible for the care in institutions of patients suffering from neurosis or psychosis. It deals with the general principles which underlie occupational therapy, the adaptation of this therapy to particular situations and full practical details as to its organization and carrying out.

La Méthode Psychanalytique et la Doctrine Freudienne. Par ROLAND DALBIEZ. Bibliothèque de Philosophie Médicale. Tome I, Exposé, pp. 656. Tome II, Discussion, pp. 528. Paris: Desclée de Brouwer. 1936. 50 Fr. each vol.

The author, who brought to the examination of psycho-analysis a philosophical training and outlook, offers here something more original and useful than the customary arguments or descriptions, wearisome in their sameness. His experience of the subject was gained in the clinic of Professor Claude, who contributes a preface. The volumes are of unequal merit. The first and less satisfying one, which the author prefers to call a *mise-en-valeur* of psycho-analysis, does not take account of modern developments of the subject, which, at any rate for English workers, are implicit in their method; introjection, for example, is barely mentioned, if at all. The exegetical second volume, therefore, in spite of its admirable and temperate review of the fundamental issues, especially those of a metaphysical nature, neglects the difficulties which the neo-Freudians know only too well: the divergencies of therapeutic method, interpretation and general doctrine which now make libidinal

development, the psycho-analysis of children, and female sexuality such controversial issues. Doctrine is less separable from method and more important than Dr. Dalbiez believes; this distinction, on which he insists, is scarcely tenable unless the treatment of neurosis in adults is the only end in view. His apologia could not be as persuasive as it is, if the doctrinal aspect and the more recent modifications and expansions of psycho-analysis had been fully handled.

Le Systeme Nerveux Vegetatif. Par J. TINEL. Paris: Masson et Cie. 1937. Pp. 847. Price 160 Fr.

This exhaustive monograph from the authoritative pen of Professor Tinel deals in detail with the anatomy and physiology of the vegetative nervous system in the light of the most recent knowledge. The pharmaco-dynamic relations of the system to the ductless glands are fully described, and the formerly debated role of the system to muscle tonus is discussed.

Further chapters deal with the chief syndromes of the system, and their treatment.

The monograph forms a valuable work of reference on its subject. It is admirably illustrated with anatomical diagrams and clinical photographs.

Psychological Studies of Human Variability. Edited by WALTER R. MILES. Psychological Monographs: Dodge Commemorative Number. Princeton: Psychological Review Co. 1937. Pp. 415. Price $4·50.

This volume of original papers is intended to commemorate the forty years of work in psychology by Professor Raymond Dodge. His earlier research into eye-movements and his lifelong concern with this subject are reflected in a number of detailed studies on visual function covering such topics as the effect of drugs on optic nystagmus, conditioned eyelid responses, the form of the vestibular eye-movement response in man, and the functional basis of spontaneous nystagmus. There are also many experimental studies dealing with the relation of muscle tone to vibratory sensibility, the adaptation times of the special senses, inhibition, and individual variations in memory and in sensitivity to vertical motion of the body. Professor Dodge's influence and activities at the Yale Institute of Human Relations may be traced in the investigations of children, coming partly from Professor Arnold Gesell and his associates, and in the more theoretical papers by Professor Kahn and others interested in medical, social or educational psychology.

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